BJS

Vol-88
No. 4-6
2001

British Journal of SURGERY

Volume 88
Number 4
April 2001

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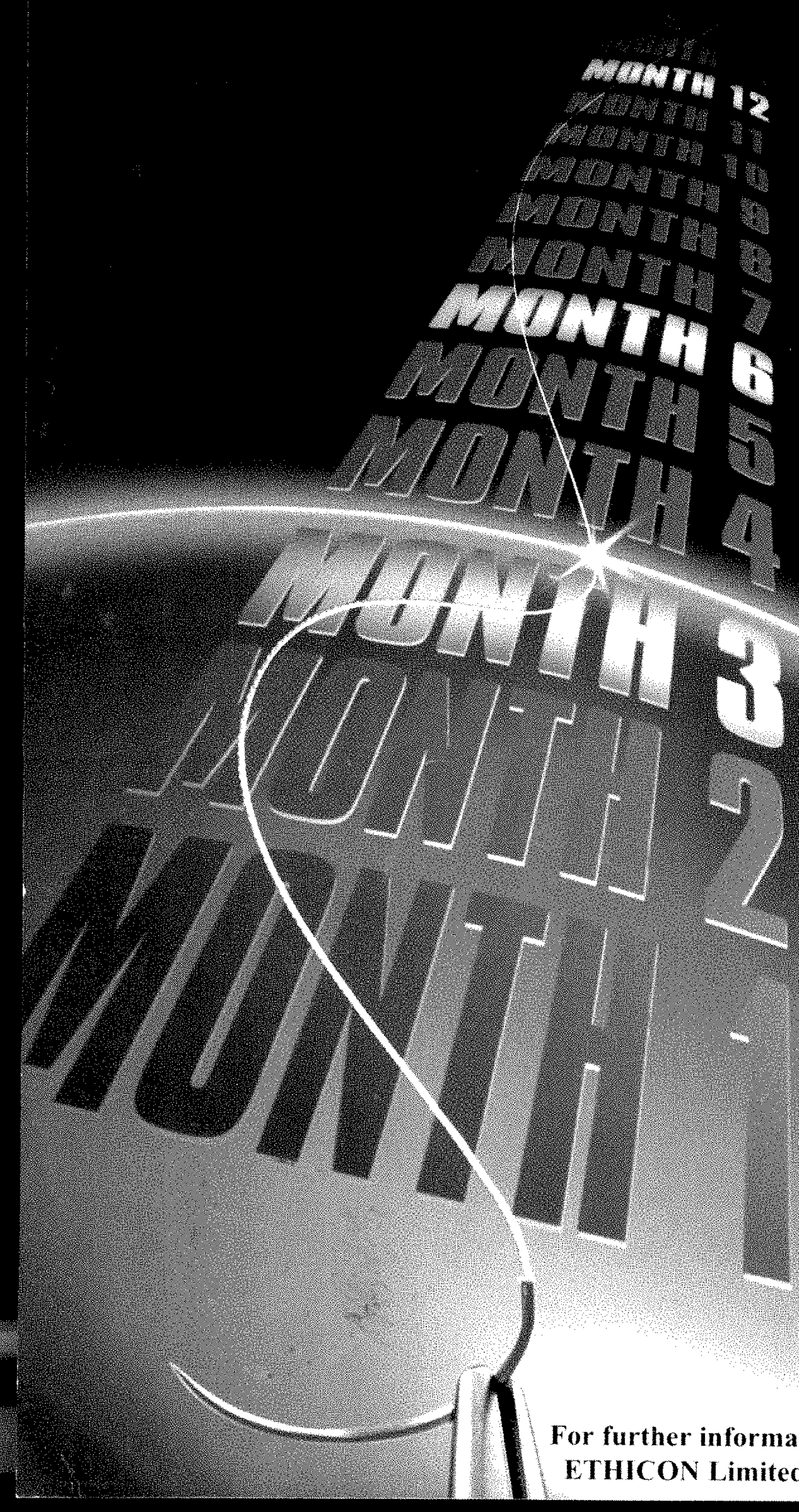

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Typeset and printed by Information Press Ltd, Oxford

*Periodicals postage is paid at Rahway, NJ and Additional Mailing offices. Postmaster: send address corrections to: the *British Journal of Surgery*, c/o Mercury Airfreight International Ltd, 365 Blair Road, Avenel, NJ 07001, USA.

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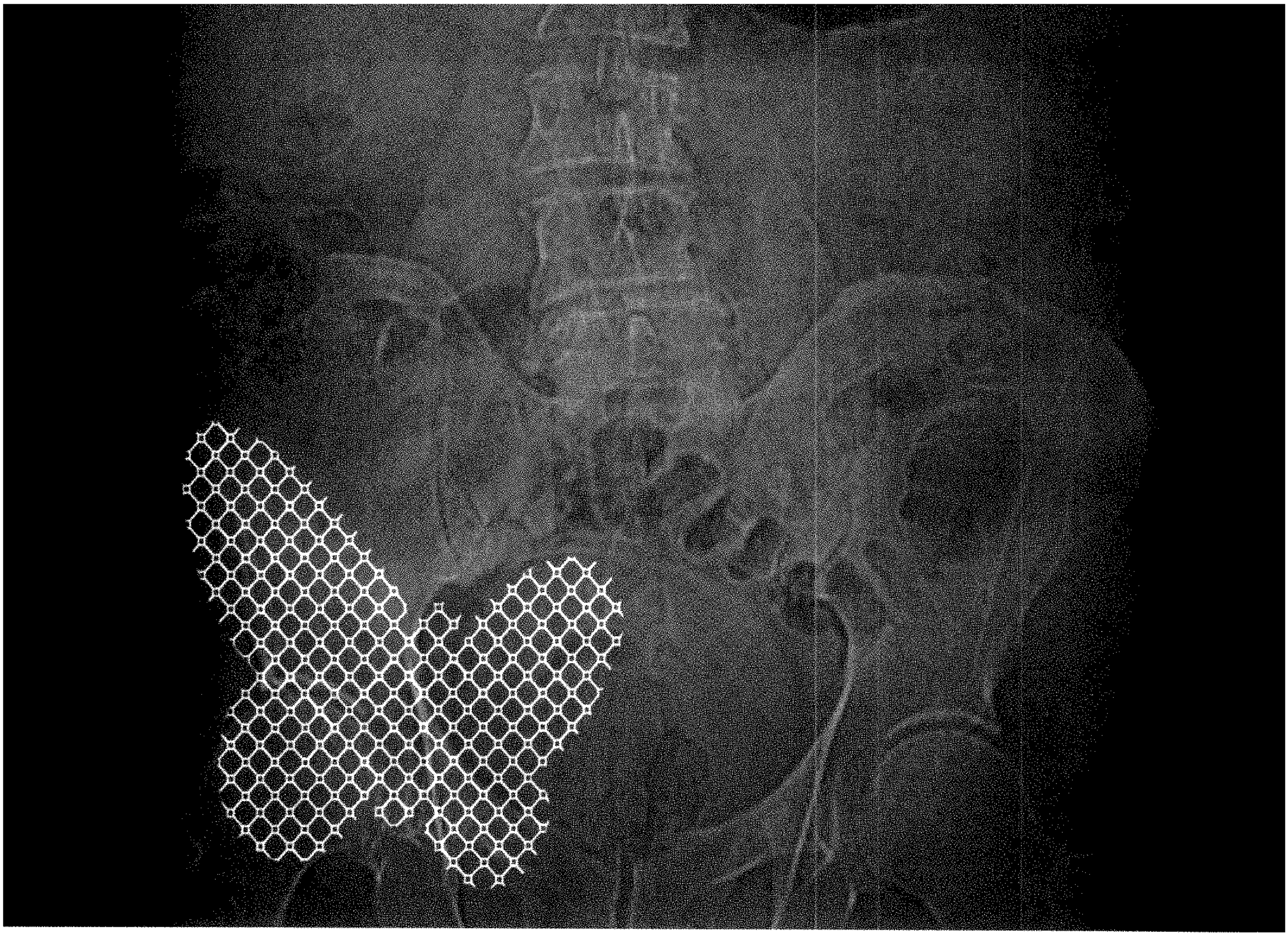

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Phaeochromocytoma in pregnancy

L. M. Brunt

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Phaeochromocytomas are uncommon tumours with an estimated frequency of less than 0·1 per cent in the hypertensive population. Characterized by a 10 per cent frequency of distribution (10 per cent extra-adrenal, 10 per cent familial, 10 per cent bilateral, 10 per cent in children and 10 per cent malignant), phaeochromocytoma may also occur coincidentally during pregnancy. Although its precise incidence in pregnancy is difficult to determine, only around 200 such cases have been reported in the world literature[1]. In a recent review of 30 246 pregnant women over 22 years of age at the Mayo Clinic, only four individuals (0·013 per cent) had adrenal tumours, two of which were phaeochromocytomas[2]. None the less, the topic of phaeochromocytoma in pregnancy is important because of the potentially lethal consequences to both the mother and the fetus if the tumour goes unrecognized.

Before the 1970s most cases of phaeochromocytoma in pregnancy were diagnosed either postpartum or at post-mortem examination. Failure to make the diagnosis before delivery has been associated with a maternal mortality rate of at least 40 per cent, with fetal death in over 56 per cent of cases[3]. However, progress has been made in recent years in terms of increased recognition and in improved methods of diagnosis, medical management and tumour localization. In a review of 139 patients with phaeochromocytoma in pregnancy, Harper and associates[1] found that the maternal mortality rate between 1980 and 1987 had fallen to 17 per cent overall, and was only 1 per cent if the diagnosis was made antepartum. Still, only about half the cases were diagnosed before delivery. Causes of maternal death in untreated cases have included stroke, cardiac arrhythmia, pulmonary oedema and malignancy.

Clinical suspicion of a phaeochromocytoma should be entertained in any patient (pregnant or not) who has hypertension and 'spells', episodic hypertension, or hypertension that occurs in the setting of a genetic predisposition to phaeochromocytoma (e.g. multiple endocrine neoplasia type 2, von Hippel–Lindau syndrome or neurofibromatosis). Hypertension due to phaeochromocytoma may be paroxysmal or sustained and is the most constant feature. Headaches are also common and may appear somewhat more frequently in the pregnant patient than in non-pregnant individuals; other symptoms may include palpitations, sweating, blurred vision, anxiety, emesis, dyspnoea and convulsions. Because some of these complaints may also appear during normal pregnancy or in patients with pre-eclampsia, suspicion of the diagnosis is often delayed. Hypertension in the patient with pre-eclampsia, however, usually develops in the third trimester and is associated with proteinuria, so phaeochromocytoma should be considered in the differential diagnosis of any pregnant patient who develops hypertension before the 20th week of gestation, who has hypertension that is not associated with protein in the urine, or who has unusual or labile hypertension.

Diagnostic evaluation of phaeochromocytoma in the pregnant patient is straightforward because maternal catecholamine levels are not normally affected by pregnancy[4]. Biochemical evaluation should begin with a 24-h urine collection for catecholamines and metanephrines. Plasma catecholamine levels obtained during a symptomatic episode may be helpful in patients with clinically suspicious symptoms but negative urinary studies. Magnetic resonance imaging (MRI) is the imaging modality of choice. MRI poses no risk to the fetus and can be used to localize both adrenal and extra-adrenal tumours. Furthermore, phaeochromocytomas have a characteristic bright appearance on T2-weighted MRI sequences. [^{131}I]*m*-iodobenzyl guanidine scintigraphy has not been evaluated in the pregnant patient and is probably contraindicated because of the potential for the agent to cross the placental barrier with unknown consequences[4].

Once a diagnosis of phaeochromocytoma in pregnancy has been made, the initial goal is to control hypertension and tachycardia pharmacologically. Prevention of hypertensive exacerbations is probably the single most important variable affecting fetal outcome as severe hypertension can result in utero placental insufficiency, early separation of the placenta and fetal death. The direct action of maternal catecholamines crossing the maternal–placenta barrier plays a less important role in fetal damage, since most maternal catecholamines are inactivated by high catecholamine degradative enzyme activity in the placenta. Alpha-adrenergic receptor blockade should be instituted with phenoxybenzamine at a low dose (10 mg three times daily), and gradually titrated upward until hypertension is controlled and the patient experiences mild orthostatic hypotension and nasal congestion. As an alternative to phenoxybenzamine, prazosin and/or labetalol can also be used for alpha blockade. Beta blockade should be reserved for patients with persistent tachycardia or tachyarrhythmias, and those with predominately adrenaline-secreting tumours. Selective beta blockade with metoprolol or atenolol is preferred as the use of long-term propranolol during pregnancy has been associated with intrauterine growth retardation. Fluids should be administered liberally during alpha receptor blockade to fill the expanded intravascular volume and to maintain a vigorous urine output. Ideally the patient should be managed in a referral centre with expertise in treating both high-risk pregnancies and the surgical, medical and anaesthetic management of phaeochromocytoma.

The timing of surgical intervention in the pregnant patient with a phaeochromocytoma must be individualized according to the adequacy of medical control of hypertension, tumour size, likelihood of malignancy and stage of pregnancy. Most groups recommend proceeding with adrenalectomy if the diagnosis is made in the second trimester, when the uterus is relatively quiescent and the risk of spontaneous abortion during surgery is low[2,4,5]. In the first trimester patients should be managed medically until the second trimester is reached, at which time adrenalectomy is carried out. If the diagnosis is made in the third trimester, surgery should be delayed until after delivery if symptoms and blood pressure can be controlled medically. The patient and fetus must be monitored closely, however, because hypertensive crises may be precipitated by haemorrhage into the tumour, labour contractions, fetal movement and even mechanical pressure from the uterus. Failure to control hypertension and evidence of malignancy on imaging studies are indications for adrenalectomy regardless of the stage of pregnancy.

The best method of childbirth in these patients is somewhat controversial. Some groups have recommended elective delivery by Caesarean section once fetal maturity has been reached, followed by adrenalectomy during the same anaesthetic[4,5]. However, if the patient is well controlled medically, a vaginal delivery may be possible[2], especially if the mother has had previous vaginal deliveries. Adrenalectomy may then be carried out at a suitable interval following recovery from childbirth.

A final consideration is the surgical method by which adrenalectomy is performed. In the 1990s, laparoscopic adrenalectomy became the preferred approach for the removal of most adrenal tumours, including phaeochromocytomas[6]. Although experience with laparoscopic adrenalectomy for phaeochromocytoma in pregnancy has been limited[7,8], there may be several advantages in using such an approach. Fernandez-Cruz and colleagues[9] showed that laparoscopic adrenalectomy for phaeochromocytoma was associated with less pronounced haemodynamic alterations and lower circulating catecholamine levels than open adrenalectomy, which in the pregnant patient might favourably impact on the outcome for both mother and fetus. Reduced postoperative pain and a faster recovery are also proven benefits of the laparoscopic approach[10]. Despite theoretical concerns about the adverse effects of carbon dioxide pneumoperitoneum on the fetus, several other laparoscopic procedures (including cholecystectomy and appendicectomy) have been carried out during pregnancy without adverse consequences for either the mother or fetus. With the lateral transabdominal approach, the laparoscopic ports are placed in the subcostal and flank region, well away from the gravid uterus. Laparoscopic adrenalectomy can be technically difficult as phaeochromocytomas may be large and vascular; indeed the vascularity of these tumours may be augmented by the effects of pregnancy itself[3,8]. It is therefore advisable that this approach is only undertaken by surgeons who are highly experienced in laparoscopic adrenalectomy techniques.

In summary, phaeochromocytoma in pregnancy is a rare condition that should be suspected in any pregnant woman with severe or unusual hypertension. Early recognition and diagnosis and a multidisciplinary team approach to management involving the obstetrician, surgeon, endocrinologist and anaesthesiologist are essential for a successful outcome. Laparoscopic adrenalectomy may offer an improved surgical management option for these patients.

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Provision of long-term vascular access for haemodialysis in a patient with exhausted superficial arm veins

A young patient is referred for permanent vascular access for haemodialysis. He has previously had multiple temporary vascular access catheters placed in the subclavian veins and bilateral failed radiocephalic and brachiocephalic arteriovenous fistulas. How should the surgeon proceed? Professor Michael Nicholson of Leicester, UK replies.

Surgeons involved in vascular access are being referred an increasing number of patients with exhausted forearm venous systems as a result of failed primary and secondary access procedures. Faced with this problem the surgeon must choose between placing a permanent central venous catheter (usually in the jugular venous system), performing an upper arm arteriovenous fistula using transposed autogenous vein, or placing a prosthetic graft in the arm or the leg. The correct choice of procedure depends on a careful preoperative assessment of the arterial inflow and venous drainage of the upper and lower limbs. However, it is also important not to discount the use of continuous ambulatory peritoneal dialysis (CAPD), even in patients who have had a number of previous failures using this technique. Many patients are labelled as having inoperable adhesions but it may still be possible to place a CAPD tube into the pelvis via a lateral rectus splitting approach through a previously unoperated site.

If CAPD is not an alternative, are the basilic and subclavian veins patent? This can only be determined by performing contrast venography or duplex scanning. The latter provides a better assessment of basilic vein patency but traditional venography is better for the subclavian vein as it is obscured from ultrasound by the clavicle. Detailed imaging should be regarded as essential, particularly in those who have had previous subclavian venous catheterization as this procedure causes significant central venous stenosis in up to 50 per cent of patients[1]. If one of the subclavian veins along with the ipsilateral basilic vein are found to be patent, the best choice for tertiary vascular access is a brachiobasilic fistula employing a vein transposition. The advantage of using the basilic vein is that it lies under the deep fascia of the arm where it is protected from damage by venipuncture. The basilic vein is mobilized out of its subfascial bed, transposed into a subcutaneous tunnel down the middle of the upper arm and then anastomosed end to side to the brachial artery. This is an underused method of permanent vascular access which has a good long-term patency rate and a low incidence of infection[2].

In many cases a brachiobasilic fistula is not an option because the ipsilateral subclavian vein is severely stenosed or occluded. In this situation the first consideration should be the use of interventional radiology to treat stenotic or occlusive venous disease by a combination of angioplasty and/or stenting. Unfortunately the long-term patency rates following these procedures are relatively poor, with a success rate of less than 30 per cent at 6 months[3]. In a number of patients the problem can be solved, at least in the medium term, if the jugular veins are patent; this allows the insertion of a cuffed tunnelled permanent central venous catheter. Still, these catheters commonly require removal for infection or thrombosis and have patency rates of less than 50 per cent at 12 months. Prosthetic brachiojugular graft fistulas offer an alternative but have been used much less and, although good early patency results have been reported[4], long-term follow-up of large numbers of procedures is awaited. It is likely that this form of access will also be prone to thrombosis and infection.

If preoperative imaging shows that the patient has a significant stenosis or occlusion of the superior vena cava, all the options described so far are precluded and attention must be turned to the legs. Again it is important to perform preoperative imaging, particularly of the venous outflow of the legs, including the saphenous, femoral and iliac veins. One difficulty the surgeon may encounter is a patient who has had temporary vascular access catheters placed in one or both femoral veins. This leaves haematomas in the groins, making any surgery more difficult and also increasing the risk of infection. The choice in these patients lies between using saphenous vein or prosthetic material such as polytetrafluoroethylene to form an arteriovenous graft in the thigh. Probably the commonest procedure in the past has been to perform a loop graft between the femoral artery and saphenous or femoral vein, but it is also possible to use a straight graft placed between the popliteal artery and the femoral vein. Thigh grafts are associated with a number of drawbacks, including a propensity to cause infection and distal ischaemia, both of which can lead to loss of limb and even loss of life. The incidence of serious infection, particularly with methicillin-resistant *Staphylococcus aureus*, is certainly much higher for grafts placed in the thigh compared with those in the arm[5]. A novel strategy that may reduce the risk of infection is to position a prosthetic loop graft between the femoral artery and vein in the subsartorial canal. This requires only a short incision in the mid thigh and allows placement of a graft in the cleaner distal thigh region.

The number of people requiring haemodialysis for end-stage renal failure continues to expand, and surgeons are being referred older and more medically challenging patients every year. There is no doubt that vascular access procedures using autogenous vein have the best patency rates and the lowest incidence of infection; a 'vein first policy' should be pursued. Perhaps the most important message is do not forget the basilic vein.

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Dysphagia after antireflux surgery

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Background: Dysphagia is experienced by many patients after antireflux surgery. This literature review examines factors associated with the development, prediction and management of postoperative dysphagia.

Methods: Published studies examining issues related to dysphagia, gastro-oesophageal reflux and fundoplication were reviewed.

Results: Postoperative dysphagia is usually temporary but proves troublesome for 5–10 per cent of patients. Technical modifications, such as a partial wrap, division of short gastric vessels and method of hiatal closure, have not conclusively reduced its incidence. There is no reliable preoperative test to predict dysphagia.

Conclusion: It is uncertain whether postoperative dysphagia arises from patient predilection or is largely a consequence of mechanical changes created by fundoplication. Anatomical errors account for a significant proportion of patients referred for correction of dysphagia but these are uncommon in large single-institution studies. Abnormal manometry cannot predict dysphagia and, on current evidence, 'tailoring' the operation does not prevent its occurrence.

Paper accepted 15 September 2000

British Journal of Surgery 2001, 88, 486–499

Introduction

The incidence of antireflux surgery is increasing despite the widespread use of proton pump inhibitors[1–3]. This is partly attributable to patient acceptance of minimally invasive surgery[4], but may also be due to the marketing of the procedure as a valid alternative to prolonged medical therapy[5]. Minimally invasive surgery is not without complications, and the management of these complications may negate the proposed cost benefit for surgery over long-term medication[6]. One of the most troublesome complications is persistent postoperative dysphagia. Although some patients experience preoperative dysphagia and many experience some degree of early postoperative dysphagia, persisting difficulties affect 5–10 per cent of patients and require surgical revision or dilatation in 1–3 per cent of cases[7–10]. This review assesses the incidence of postoperative dysphagia, examines factors associated with its development, and considers methods of prevention and management.

Methods

A computerized Medline search was performed with the key words 'fundoplication' and 'gastro-oesophageal reflux' combined with 'dysphagia' for the period January 1985 to January 2000. The bibliographies of the retrieved articles were reviewed to obtain other relevant papers. A manual search of abstracts published in *Gastroenterology* was undertaken for 1998 and 1999. Abstracts are referenced only if they report new material or the results of randomized controlled trials. Articles are restricted to those written in English. Outcome after surgery for giant hiatus hernia or Collis gastroplasty is not examined. The role of antireflux surgery for patients with scleroderma or other connective tissue disease, and after myotomy for achalasia or Chagas disease, is also not examined.

There has been a slow improvement in the quality of available research with an increasing number of well conducted randomized controlled trials and prospectively determined outcome audits. However, many papers still have serious deficiencies, including lack of independent follow-up and unspecified measurements for dysphagia. For these reasons, it is likely that the incidence of postoperative dysphagia is under-reported in many papers. The effect of different systems of measurement of dysphagia has been demonstrated in a trial evaluating the effect of division of short gastric vessels[11]. Four methods were used, resulting in an incidence of dysphagia in one group of 15, 17, 56 or 74 per cent, depending on the chosen system.

Preoperative dysphagia

Excluding patients with an oesophageal stricture, dysphagia occurs in 20–50 per cent of patients before antireflux surgery[9–13]. This preoperative symptom is improved in most patients after antireflux surgery[9,12,14–16], although new or worse dysphagia is noted in 2–14 per cent[12,15,16]. Difficulty in swallowing occurs frequently with reflux disease, although it is often not reported or recognized by patients owing to modification of diet or eating habits[17]. In non-surgical populations, the incidence of dysphagia, as distinct from odynophagia, is not well recorded[18,19]. In a retrospective study, El-Serag and Sonnenberg[6] reported an incidence of dysphagia of 3 per cent in 29 514 patients without stricture or ulcerative oesophagitis, and 13 per cent in 5064 patients with these complications. Triadafilopolous[20] reported an incidence of 47 per cent in patients with erosive oesophagitis. Possible mechanisms of preoperative dysphagia include the presence of a hiatus hernia[21–23], impaired primary peristalsis[24], impaired secondary peristalsis[25,26], oesophageal inflammation[27–29], hypersensitivity to acid[20,30] and lowered sensory threshold to a bolus[31]. It is possible that some of these characteristics would make patients unsuited to fundoplication.

Whether preoperative dysphagia correlates with postoperative dysphagia has, surprisingly, been evaluated infrequently. Rydberg *et al.*[13] and Gotley *et al.*[32] found no correlation between preoperative and postoperative dysphagia. Beckingham[33], while commenting on a previous study[34], also reported no relationship.

Mechanism of dysphagia after fundoplication

Technical errors and surgical complications account for a proportion of early postoperative dysphagias. These problems are mainly anatomical and include an excessively tight fundoplication, a twisted fundoplication, a slipped fundoplication, paraoesophageal herniation or hiatal stenosis[1,35–39]. However, the majority of patients with transient dysphagia have no identifiable cause. It is suggested that temporary dysphagia may be attributable to oesophageal oedema[40], stretching[41] or temporary hypomotility[42,43].

Fundoplication increases the length of a high-pressure zone at the oesophagogastric junction. Although this is frequently described as the 'lower oesophageal sphincter' (LOS)[44,45], this is incorrect terminology as intrinsic sphincter function makes only a small contribution to the oesophagogastric junction pressure after fundoplication[46]. Fundoplication also increases the resting pressure of this LOS[44,47,48] and increases residual (nadir) pressure on swallowing[47–49]. The increase in LOS pressure arises from the extrinsic mechanical compression of the wrap, which can be demonstrated *in vivo*[50,51] and *ex vivo*[52], and also from hiatal closure[46]. Fundoplication maintains the length of the LOS during gastric distension[45] and it is observed that, as gastric pressure increases, the fundoplication imparts a proportionally greater radial force to the oesophagus with the observed LOS pressure double that of intragastric pressure[52]. It is hypothesized that this higher pressure occurs because of the shorter radius of curvature of the wrap than the gastric body[52]. This increased pressure gradient created by fundoplication improves retrograde competence[45,50,52], possibly at the expense of compromising antegrade flow[53] and so may result in dysphagia.

Other observed consequences of fundoplication include impaired LOS relaxation secondary to oesophageal distension[54] and changes in the velocity of oesophageal peristalsis[47]; however, overall peristaltic function is improved[54–57]. Kahrilas *et al.*[21,53,58] have investigated the mechanisms of swallowing and the effect that fundoplication has on bolus transport across the oesophagogastric junction. This region differs from the tubular oesophagus where a bolus propagates as the result of luminal closure from circular muscle contraction, accompanied by longitudinal muscle contraction resulting in a stripping peristaltic wave. The oesophagogastric junction and phrenic ampulla rely on shortening of the longitudinal muscle to elevate the oesophagus and then recoil, owing to a combination of longitudinal muscle relaxation and the effect of oesophageal attachments, such as the phreno-oesophageal ligament. Emptying of the phrenic ampulla occurs during expiration. Fundoplication interferes with this process by preventing axial movement of the oesophagogastric junction and by limiting the opening dimensions of the squamocolumnar junction[53]. The consequence of this is raised intrabolus pressure[53,59,60]. If the oesophageal muscle cannot increase its tone sufficiently to overcome this pressure, failure of oesophageal emptying occurs[53] and the oesophagus exhibits repetitive sustained contraction[53,61,62]. However, correlation of these findings with clinical dysphagia has not yet been reported.

Another consequence of fundoplication is an inhibition of spontaneous transient LOS relaxation[49,50]. This may result from the wrap preventing shortening of the LOS[45] or limiting fundic distension, a major stimulus for transient LOS relaxation [63]. However, oesophageal mobilization and short gastric vessel division without fundoplication also inhibits transient LOS relaxation[50]. This suggests that operative dissection may injure neural control mechanisms as transient relaxation is vagally mediated[63,64]. However, swallow-induced LOS relaxation is not affected by sham fundoplication[50], so mechanical factors rather than neural injury appear to be more important in the causation of postoperative dysphagia.

Incidence of postoperative dysphagia

The incidence of postoperative dysphagia, as recorded in the literature, is extremely variable. Data from open antireflux procedures suggest rates of 2–44 per cent[65,66]. In addition to the previously mentioned influence that scoring system and scorer have on recorded rate, the time at which the measurement is taken also influences the rate. Dysphagia is very common immediately after surgery and decreases over 3–6 months. A review of outcome after laparoscopic fundoplication was performed by Perdikis *et al.* from 1991 to1995[7,8]. The results of this review are shown in *Table 1*, along with results for dysphagia from subsequent large open or laparoscopic prospective series. In series presenting several measures of dysphagia, dysphagia to solids is chosen to represent incidence.

Operative factors influencing postoperative dysphagia

The original Nissen fundoplication was 4–6 cm long and snug around the oesophagus[74]. DeMeester *et al.*[75,76] and Donahue *et al.*[77] introduced the concept of a short, floppy fundoplication. Techniques other than a 360° fundoplication include the posterior Toupet[78], Lind[79] or Guarner[80] fundoplication, the transthoracic Belsey Mark IV procedure, an anterior Dor, Watson[81,82] or Thal fundoplication, and a Hill repair[83]. These operations, as performed today, sometimes bear little resemblance to their original descriptions[71]. Laparoscopic fundoplication was first reported in 1991[84,85] and has enabled a concentration of operative expertise with a concomitant interest in conducting randomized controlled trials examining technical factors and their influence on outcome.

Laparoscopic *versus* open surgery

Three published randomized controlled trials compare open with laparoscopic surgery[86–88]. Heikkinen *et al.*[86] claim an increase in postoperative dysphagia with the latter but do not provide the data to assess significance. Laine *et al.*[87] demonstrated no difference in dysphagia (open 13 per cent, laproscopic 16 per cent). The results of a multicentre randomized controlled trial of 103 patients show a significant difference in dysphagia rate at 3 months (open 0 per cent, laproscopic 12 per cent)[88]. However, two other trials, as yet reported only in abstract form, suggest no difference in rates of postoperative dysphagia[89,90].

Non-randomized data also provide conflicting information. Peters *et al.*[91] demonstrated a non-significant difference (open 3 per cent, laparoscopic 9 per cent), which was associated with higher residual LOS pressure measurements in the laparoscopic group. Rantanen *et al.*[92] demonstrated a significant difference for temporary dysphagia (open 41 per cent *versus* laparoscopic 67 per cent; $P = 0.05$)

Table 1 Dysphagia after fundoplication

			Incidence of dysphagia (%)				Intervention for dysphagia (%)	
Reference	Year	No. of patients	Preop.	Early (< 3 months)	Intermediate (3–6 months)	Late (> 6 months)	Endoscopy	Reoperation
Perdikis *et al.*[7]*	1997	2068		20		6	4	1
Perdikis *et al.*[8]*	1996							
Watson *et al.*[67]	1996	174		20	11	6	2	3
Hunter *et al.*[68]	1996	184		28	5		3	0
Gotley *et al.*[9]	1996	200	54		17	36	3	1
O'Reilly *et al.*[69]	1996	100		4	2	0	2	0
Watson *et al.*[11]	1997	102	33	56	48		3	2
Anvari and Allen[10]	1998	381	54		14	7	2	0
Kiviluoto *et al.*[70]	1998	200	30	19		2		2
Patti *et al.*[71]	1998	201			5		2	
Dallemagne *et al.*[72]	1998	622	38	100	12	2	2	1
Rydberg *et al.*[13]	1999	106	20			8		
Watson *et al.*[73]	1999	107	26		25			3
Franzen *et al.*[16]	1999	101	66			11		
Soper and Dunnegan[35]	1999	290				7	2	
Bohmer *et al.*[12]	2000	106	27			18	2	
Total		4942	41	34	14	6	3	1

*Review of outcome after laparoscopic fundoplication from 1991 to 1995 but not for persistent dysphagia (open 18 per cent, laparoscopic 20 per cent). Four other trials failed to demonstrate any difference[2,93–95]. The reasons suggested to explain the higher incidence of dysphagia after laparoscopic surgery in some series include greater oesophageal trauma owing to impaired tactile feedback, less fundal mobilization, especially with non-division of short gastric vessels[86], and spatial differences resulting in the creation of a smaller posterior window[92]. However, many of these series were conducted during the early experience with laparoscopy and the difference in dysphagia rates may be associated with a learning curve, although surgical inexperience does not seem to correlate with dysphagia[37,96].

Type of antireflux procedure

The rationale for performing a partial fundoplication is to reduce the resistance to bolus transport noted after a Nissen fundoplication, thus reducing the risk of dysphagia. Manometric measurements demonstrate lower resting LOS pressure and lower nadir pressure after anterior[73] and posterior[97,98] fundoplication than after Nissen fundoplication. While there is some concern that partial fundoplication procedures fail to control reflux adequately[99], several studies describe good long-term results[16,81,100]. Anatomical models comparing yield pressure demonstrate similar results for Nissen and Toupet fundoplications[51,52], although the Toupet procedure permits reflux at low intragastric pressure[52,101] and this is thought to permit gastric venting, perhaps reducing the incidence of gas bloat[98].

Few randomized controlled trials have compared methods of fundoplication; most have small numbers and have provided inconclusive or disputed results (*Table 2*). For instance, the study by Thor and Silander[102] contained only 12 patients in the Nissen fundoplication arm; one-quarter of these patients developed paraoesophageal herniation and accounted for the high rate of dysphagia. The larger randomized studies suggest that posterior fundoplication has a similar rate of dysphagia to Nissen fundoplication[13,97]. Anterior fundoplication (180°) has been compared with Nissen fundoplication by Watson *et al.*[73], with the finding that anterior fundoplication decreases the incidence of postoperative dysphagia at 6 months. Long-term follow-up in this cohort of patients is awaited to assess the durability of anterior fundoplication for control of gastro-oesophageal reflux. The most significant difference between groups after operation was with respect to dysphagia to lumpy solids, although other variables used to measure dysphagia also supported a better outcome for anterior fundoplication. There was a near significant difference ($P = 0{\cdot}07$) in preoperative dysphagia to lumpy solids between groups in this study but, as stated previously, no study has yet demonstrated any correlation between preoperative and postoperative dysphagia; it would be wise to evaluate this more rigorously.

Non-randomized comparative series are flawed as the decision to perform an antireflux procedure is made according to chronology[68], surgical preference or is 'tailored' because of suspicion of dysmotility[107] (*Table 3*). Other variations in operative technique, such as fixation of the fundoplication by a 'hiatopexy' or the use of 'crown' sutures, have not been compared with control groups.

Division of short gastric vessels

There are two published randomized controlled trials and one abstract that assess the effect of division of short gastric vessels on postoperative outcome[11,112–115]. Pooled data from these trials are shown in *Table 4*. The two published series[11,114] record no difference in outcome in terms of dysphagia. Luostarinen and Isolauri[115] noted an increased

Table 2 Randomized controlled trials comparing methods of fundoplication

Reference	Year	No. of patients	Open or laparoscopic	Comparison with Nissen	Postoperative dysphagia (%)	
					Early	Late
DeMeester *et al.*[41]	1974	45	Open	Belsey and Hill	N 87, H 87, B 40	All groups 0
Thor and Silander[102]	1989	31	Open	Toupet	—	N 33, T 10
Walker *et al.*[103]	1992	52	Open	Lind	N 31, L 23	N 8, L 15
Lundell *et al.*[97]	1996	107	Open	Toupet	N 47, T 21	N 9, T 7
Lundell *et al.*[104]	1991					
Laws *et al.*[105]	1997	39	Laparoscopic	Toupet	—	N 0, T 0
Watson *et al.*[73]	1999	107	Laparoscopic	Anterior	N 40, A 15	—
Anderson *et al.*[106]	1998					
Rydberg *et al.*[13]	1999	106	Laparoscopic	Toupet	—	N 10, T 6

N, Nissen; H, Hill; B, Belsey Mark IV; T, Toupet; L, Lind; A, anterior incidence of recurrent hiatus hernia in patients undergoing fundal mobilization, although this is likely to have arisen because of failure to close the hiatus. In contrast, Dalenbäck *et al.*[113] demonstrated a significant reduction in dysphagia with fundal mobilization and a lower operative failure rate. Despite the pooled data suggesting a significant advantage in favour of short gastric vessel division, these results arise because of inclusion of the abstract by Dalenbäck *et al.*[113]. Publication of this study, along with long-term follow-up from the trial by Watson *et al.*[11], should help clarify the role of short gastric vessel division.

DeMeester *et al.*[76], in a series of 100 consecutive patients, felt that the addition of fundal mobilization was helpful in reducing the incidence of postoperative dysphagia after demonstrating that patients with fundal mobilization had complete manometric relaxation of the LOS on swallowing, unlike those without fundal mobilization. However, this technical modification was undertaken at the same time as a reduction in the length of the wrap and was not tested independently. In contrast, Luostarinen *et al.*[114] demonstrated slower oesophageal emptying 3 days after division of short gastric vessels, an effect not found in the group with intact short gastric vessels. At the outset of laparoscopic fundoplication, surgeons often avoided division of short gastric vessels. High rates of postoperative dysphagia led to reassessment of operative technique with subsequent division, resulting in lower rates of dysphagia[32,68,71,72]. Whether this constitutes evidence or merely reflects learning curve bias is unclear. Attempts to wrap an immobile fundus around the oesophagus may result in a twisting deformity[68]. However, the randomized trials have demonstrated that it is possible to achieve tension-free wraps without the division of the short gastric vessels. The important technical element appears to be the creation of a floppy wrap, which requires fundal mobilization in some cases.

Hiatal closure

There is increasing recognition of the importance of the diaphragmatic crura in the antireflux mechanism, especially during inspiration and straining[46,116–118]. Despite this, many surgeons have elected to forego hiatal repair during early laparoscopic procedures, resulting in an incidence of up to 10 per cent of wrap herniation or paraoesophageal herniation[1,36,119]. This complication may result in recurrent reflux or dysphagia. However, closing the hiatus also may contribute to postoperative dysphagia[120]. It is suggested that part of the problem is related to oesophageal angulation created by a long posterior repair. Anterior closure has been compared with posterior closure in 77 patients in a randomized trial, and reported in abstract

Table 3 Non-randomized trials comparing methods of fundoplication

Reference	Year	No. of patients	Comparison with Nissen	Postoperative dysphagia (%)
Hunter *et al.*[68]	1996	129	Toupet	N 17, T 16
Bell *et al.*[108]	1996	22	Toupet	N 36, T 0
Karim *et al.*[109]	1997	83	Toupet/anterior	Early N 17, P 8 Late N 7, P 10
Coster *et al.*[110]	1997	226	Toupet	N 6, T 0
Wetscher *et al.*[24]	1997	49	Toupet	N 6, T 3
Civello *et al.*[111]	1997	72	Hill	Early N 25, H 18 Late N 25, H 5

N, Nissen; T, Toupet; H, Hill; P, partial fundoplication

Table 4 Proportion of patients with dysphagia after fundoplication, with or without division of short gastric vessels

				Proportion with dysphagia		
Reference	Year	No. of patients	Follow-up (months)	Division	No division	*P*
Watson *et al.*[11]*	1997	102	6	15 of 51 (29)	16 of 49 (33)	n.s.
Luostarinen and Isolauri[115]†	1999	50	36	2 of 26 (8)	6 of 23 (26)	n.s.
Dalenbäck *et al.*[113]	1999	100	12	10 of 50 (20)	18 of 50 (36)	0·02
Total		249	—	27 of 127 (21)	40 of 122 (33)	0·04‡

Values in parentheses are percentages. *Two patients lost to follow-up at 6 months, considered dysphagia to lumpy solids; †one patient lost to follow-up, considered dysphagia of new onset or worse than before operation. n.s., Not significant. ‡χ^2 test form[121]. Postoperative dysphagia scores were similar between groups but a greater number of posterior repairs required operative revision because of a 'tight hiatus' diagnosed by postoperative barium swallow[121].

Bougie size and length of wrap

DeMeester *et al.*[76] demonstrated a reduction in temporary postoperative dysphagia in 100 consecutive patients by increasing the bougie size from 36 to 60 Fr. Persistent dysphagia was reduced in the same group by decreasing the wrap length from 4 to 1 cm. These technical aspects have been widely adopted and most surgeons now perform a 1–2-cm fundoplication over a 48–60-Fr bougie[9,15,68], although there is little confirmatory evidence to support the use of a bougie in addition to a floppy wrap. The anterior wall of the fundus is more compliant than the posterior wall in explanted cadaver stomachs, theoretically permitting a 'floppier' fundoplication[101], but the clinical relevance of this is unclear. One randomized trial[122], reported in abstract, compares the use of a 56-Fr bougie with fundoplication without a bougie. A significant difference in postoperative dysphagia was noted at 3 months (18 per cent bougie, 30 per cent no bougie) but recalculation using the data available in the abstract suggests that this not a statistically significant difference ($P = 0{\cdot}07$)[122].

Intraoperative manometry

Calibration of the wrap during operation is an attractive proposition. Several authors support intraoperative manometry for partial and total fundoplication procedures, and believe it is an important element in minimizing recurrent reflux[111,123–125]. Del Genio *et al.*[124] demonstrated that a 'hypercalibrated' wrap was necessary to prevent recurrent reflux, but this was at the expense of an increased rate of postoperative dysphagia. The use of intraoperative manometry is not widespread because the reliability and accuracy of recordings under anaesthesia is doubtful[126,127]. Although patients are unable to swallow, LOS relaxation can be elicited in response to an oesophageal balloon under anaesthesia, but operative dissection and performance of a fundoplication severely impairs this response[127].

Prediction of postoperative dysphagia

Few studies have examined patient factors that have a potential to affect outcome. Theoretically, elderly and diabetic patients may be more likely to experience postoperative dysphagia. The elderly have impaired secondary peristalsis[128] yet appear to have similar rates of postoperative dysphagia to those of younger patients[129]. Raised blood sugar level increases oesophageal sensation to a distending stimulus[130] and, even in the absence of a demonstrated autonomic neuropathy, diabetes mellitus is associated with peristaltic failure and impaired oesophageal transit[131]. Oesophageal inflammation impairs primary[47,132] and secondary[26,133] peristalsis but clinically there is no correlation between grade of oesophagitis and postoperative dysphagia[32,134]. Patients with hiatus hernia have impaired LOS function, and impaired acid clearance and oesophageal transit, which worsen with increasing hernia size. However, fundoplication seems to correct these deficits[23].

Psychological factors are related to patient satisfaction after operation, but do not correlate with persistent dysphagia[135]. Kamolz *et al.*[136] hypothesized that patients' eating habits contributed to the presence of troublesome early dysphagia. To evaluate this they used a test designed to measure the 'locus of control', which represents the amount of influence that patients feel they have over their outcome. Those who believed they had external control of their outcome had a significantly lower rate of dysphagia than those who believed that their outcome depended on fate or chance. This difference was present from 1 week to 3 months after surgery. If postoperative dysphagia is due to pre-existing oesophageal factors, it should be possible to detect these using preoperative oesophageal function tests. The ability of preoperative oesophageal manometry and transit studies to predict postoperative dysphagia is discussed below.

Manometry

Non-specific and often contradictory manometric findings, including impaired LOS function and peristaltic dysfunction, occur frequently in association with gastro-oesophageal reflux[132,137,138]. Peristaltic dysfunction is considered by some surgeons to be a contraindication to total fundoplication[139]. However, the available evidence suggests that there is no correlation between abnormal primary peristalsis and postoperative dysphagia[10,32,34,56,57,59,100,140]. Disordered peristalsis often improves after operation and total fundoplication has been performed even in the presence of aperistalsis, without dysphagia resulting[34,56].

Conventional manometry analyses oesophageal response to swallowing a bolus of water. Most patients with dysphagia have greater problems swallowing solids. Therefore the use of a solid or semisolid bolus, or manometric measurements such as intrabolus pressure and secondary peristaltic function, may reflect the situation more accurately. However, the use of solids during manometry has proved difficult to standardize and interpret[141–143]. The measurement of secondary peristalsis is also still largely experimental and has not reached the stage of routine clinical application[26,144,145]. Ramp pressure, a representation of intrabolus pressure[146], is measured as the plateau pressure of the initial upswing of the manometric tracing just before the peristaltic wave contraction[59,106]. This pressure is increased by fundoplication[53]. Only one study[59] has examined preoperative ramp pressure in the context of postoperative symptoms; it found no relationship with dysphagia. In the context of gastro-oesophageal reflux, manometry is useful to exclude disorders such as achalasia or diffuse oesophageal spasm[141,147,148] but, as it is currently performed, it provides little aid in prediction of postoperative dysphagia.

Oesophageal transit studies

An alternative measurement of oesophageal function is the time taken for bolus transport. Such transit studies may use solid or liquid boluses labelled with radionuclide or barium. These investigations have the advantage of being less invasive than manometry with greater patient acceptance. Only three studies have used oesophageal transit as a predictive strategy[149–151]. Hunt *et al.*[149] used a technetium-labelled gelatin bolus and demonstrated that slow oesophageal transit (more than 24 s) was predictive of postoperative dysphagia, although only a small number of patients was studied. Lundell *et al.*[150] used technetium-labelled minced beef, which was masticated before swallowing. Delayed transit (more than 93 s) was correlated to preoperative dysphagia, but was not predictive of postoperative dysphagia. Russell *et al.*[151], using a technetium-labelled water bolus, also demonstrated that prolonged transit (more than 15 s) was correlated with preoperative dysphagia but not with postoperative dysphagia.

Oesophageal transit time is dependent on bolus viscosity[152,153], composition and volume, and on patient position[142] and oesophageal acidification[154]. It is impaired in patients with gastro-oesophageal reflux in comparison to controls[55,155]. Reference values for oesophageal transit need to be defined in each centre, with demonstration of reproducibility before routine clinical use. It is possible that oesophageal transit might replace manometry as a screening test for achalasia or diffuse oesophageal spasm[156,157]. Its role in predicting postoperative dysphagia requires further investigation.

Gastric emptying studies

Theoretically, delayed gastric emptying could provoke postoperative dysphagia by increasing intragastric pressure, with a subsequent increase in wrap pressure around the LOS which could impede bolus passage into the stomach[52]. Preoperative gastric emptying is normal in most patients with gastro-oesophageal reflux[158,159]. Fundoplication usually increases the rate of gastric emptying[159,160]. It is suggested that postoperative symptoms may be related to failure to enhance gastric emptying[161]. However, in a study that specifically examined dysphagia, the postoperative emptying rate was not related to dysphagia[162]. This suggests that preoperative delayed emptying was associated with early postoperative dysphagia but not with long-term symptoms.

Findings in patients who develop dysphagia

Details of the causes of postoperative dysphagia differ depending on the origin of the report, duration of follow-up and methods of data collection. Patients referred to a tertiary referral centre differ from those in a prospective audit. Reports arising from surgical or gastroenterological units also differ in aim and available intervention.

Anatomical findings

Peptic strictures occur in a small number of patients after fundoplication[163]. Other anatomical problems resulting in dysphagia include paraoesophageal herniation, slipped fundoplication, hiatal stenosis and a rotational deformity of the oesophagus[1,35–39]. Structural failure of the fundoplication occurs in 1–9 per cent of cases[1,35,36,71], although this may increase over long-term follow-up[164] and be greater in low-volume centres[66]. Only about one-third of these anatomical complications results in dysphagia[36,71]. Many patients remain asymptomatic or present with symptoms of recurrent reflux or chest pain. Correction of a demonstrated structural defect results in resolution of dysphagia in most instances[1]. Anatomical errors in fundoplication should be preventable. They are uncommon in recent prospective series from high-volume centres but have accounted for over 50 per cent of patients with persistent postoperative dysphagia referred for correction to a tertiary referral institution[36].

Manometric findings

Several studies have compared patients who developed dysphagia after fundoplication with those who did not. Anvari and Allen[10] found higher mean LOS basal and nadir pressures in the group experiencing dysphagia after fundoplication. The finding of raised nadir pressure in association with dysphagia has been confirmed by other groups[59,60,165,166], although the correlation is often weak[59,106] and not universally demonstrated[54].

Oesophageal ramp pressure, as a measure of outflow resistance, may correlate with postoperative dysphagia[60,106,165,166]. Unfortunately, many of these studies are available only in abstract form at present, contain small numbers of patients, and often combine patients with dysphagia with those presenting with other symptoms after antireflux surgery. The largest published series evaluating ramp pressure did not demonstrate a correlation with postoperative dysphagia[59].

There is no difference in oesophageal body primary peristalsis[10,54,167] or secondary peristalsis[54] between patients with and without dysphagia. Some authors have reported an 'achalasia-like' pattern in those with dysphagia after antireflux surgery despite normal preoperative manometry findings[168,169]. This terminology implies neurological changes or injury to the LOS, whereas the manometric features possibly represent a tight fundoplication with the associated peristaltic dysfunction a result of outflow obstruction.

Management of dysphagia

The management of dysphagia relies on level 4 evidence (expert opinion) at best. The majority of patients with dysphagia will improve. This usually occurs by 3 months after operation[68]. These patients require dietary advice and reassurance; they are at risk of bolus obstruction if they fail to adhere to a soft diet initially. Observation of eating patterns and behavioural assessment, combined with psychological support, may prove useful for some[136].

Excessive weight loss and inability to tolerate liquids are of greater concern. For those with early severe dysphagia, a Gastrografin® (Schering, Berlin, Germany) or barium swallow is the most common initial investigation[36,139]. Some centres perform radiographic contrast studies routinely after surgery to enable early laparoscopic revision before the development of adhesions[67]. It is possible that some patients undergo unnecessary procedures because they might improve without active intervention. Endoscopy can demonstrate anatomical derangement, but this may be difficult to interpret[170]. It may be better than contrast radiology at predicting a disrupted wrap but worse at predicting one that is too tight[171]. The investigations appear complementary[163] and both should be performed. If no anatomical reason for failure is revealed, repeat manometry may demonstrate increased LOS nadir pressure[172] although, as discussed previously, the importance of these findings is not clear.

Pneumatic dilatation with a 30–40-mm balloon or bougienage has been used in a subgroup of patients with no identified cause of dysphagia, with relief being obtained in about 50 per cent[163,168,172]. Most patients respond to the initial dilatation[68,172], although the procedure is usually repeated if there is a suboptimal response. Dilatation is more likely to be successful in those with normal peristalsis[172] and an intact fundoplication[163]. Anatomical problems are best corrected surgically[36]. In the case of hiatal stenosis, the fundoplication can be left intact[39]. In the absence of a demonstrated anatomical reason for failure and after failed dilatation, patients with residual problems may benefit from revision from a total to a partial fundoplication[173]. The use of LOS myotomy in the absence of definite achalasia in patients with a refractory problem has been reported[1].

Patients who develop dysphagia after Heller myotomy for achalasia are often treated with prokinetic agents. The efficacy of these medications in the context of postfundoplication dysphagia is not yet clear.

Conclusions

Dysphagia is a common symptom associated with gastro-oesophageal reflux and is usually significantly improved after antireflux surgery. However, in the early postoperative period a majority of patients experience difficulty with swallowing. Forewarned, and with dietary modification, many tolerate this temporary dysphagia with few complaints. A small group of patients, whether due to unrealistic expectations, oesophageal hypersensitivity or personality factors, find the temporary postoperative dysphagia intolerable despite explanation and reassurance. Apart from ensuring a loose wrap, and a non-obstructing hiatal closure, there is little evidence to suggest that other interventions can reduce the incidence of temporary dysphagia. Results of randomized trials comparing total and partial fundoplication confirm less early dysphagia after a posterior wrap but no difference in late dysphagia[104], and no early difference after an anterior wrap, but some benefit in intermediate dysphagia[73]. Identification of patient-related factors that differentiate those with troublesome dysphagia from those who are untroubled may help select those likely to develop problems and enable the introduction of preventive strategies or more accurate preoperative counselling.

Dysphagia that fails to resolve is troublesome. Anatomical errors certainly account for a proportion of cases of non-resolving postoperative dysphagia but are uncommon in prospective series from high-volume centres. Experimental work demonstrates that the creation of a fundic wrap and hiatal repair prevents normal oesophageal axial excursion during swallowing. These factors may be related to dysphagia, but do not explain why only a small proportion of patients develop a persistent problem. Whether pre-existing or iatrogenic, oesophageal motility problems, with an inability to overcome the fixed, relatively high nadir pressure created by fundoplication, appear to be the most likely explanation for dysphagia. There is no reliable test at present to predict those likely to experience long-term difficulty in swallowing. Abnormal conventional manometry does not correlate with postoperative dysphagia. This suggests that either the wrong aspects of oesophageal function are being examined, or that dysphagia is not a consequence of preoperative variables, but arises from operative technique. Further investigation of patients experiencing postoperative problems may help clarify mechanisms and identify predictive strategies. A unified approach to the measurement and reporting of postoperative dysphagia would help greatly in improving research in this field.

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Management of aortic aneurysm in the presence of a horseshoe kidney

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Background: The coexistence of an aortic aneurysm and a horseshoe kidney poses a technical challenge to the vascular surgeon at the time of aneurysm repair. The aim of this review is to develop a guideline for the treatment of patients with this dual pathology.

Method: A literature review combined with local experience provided a total of 176 cases. These were divided into two groups: asymptomatic aneurysms (134) and ruptured aneurysms (42), both in combination with a horseshoe kidney.

Results: Six types of operative approach were described: transperitoneal approach with or without separation of the renal isthmus, retroperitoneal approach, placement of a stent-graft, aneurysmal wrap and exploration without exclusion of the aneurysm. Diagnosis of the horseshoe kidney was made before operation in 81 per cent of patients in the asymptomatic group, and in 55 per cent (23 of 42) in the ruptured group. Computed tomography proved to be the most reliable diagnostic procedure. Occlusion of renal arteries originating from the aneurysm was reported in 51 per cent in the asymptomatic group, and in 74 per cent (23 of 31) in the ruptured group.

Conclusion: The preferred surgical options for asymptomatic patients with an aortic aneurysm and a horseshoe kidney are the placement of a stent-graft or a retroperitoneal approach; both avoid many of the technical difficulties related to the presence of the horseshoe kidney. The approach of choice for a ruptured aneurysm is transperitoneal. Separation of the renal isthmus should be avoided.

Paper accepted 2 November 2000

British Journal of Surgery 2001, 88, 500–509

Introduction

The commonest anatomical variation of the kidney is the horseshoe kidney. It represents a fusion anomaly, mainly at the lower poles, that occurs between the fourth and sixth week of gestation. The isthmus connecting the lower poles may be a fibrous band or may contain functional parenchyma[1]. Horseshoe kidneys show great variation in origin, number and size of renal arteries and veins; only 30 per cent of all horseshoe kidneys have a single renal artery to each side[2]. The combination of such a renal anomaly with an aortic aneurysm presents a diagnostic and therapeutic challenge to the vascular surgeon. This article describes the published experience of this situation and comments on the consequences of the variations that might be encountered with this interesting dual pathology.

Method

A Medline search carried out using the keywords horseshoe, kidney and aneurysm revealed 78 publications. The references from these publications revealed a further 11 publications. A total of 89 publications[3–91] describing one or more cases of an aortic aneurysm in combination with a horseshoe kidney was therefore considered. No limit was set to the year or language of publication. One overlapping report[91] was found and excluded, leaving 88 publications[3–90] to be reviewed. The authors' own experience, consisting of two cases, was also included.

All publications were studied for the following variables: year of publication, country and number of cases of aortic aneurysm with a horseshoe kidney. The following variables were recorded for the individual cases: sex and age of the patient, complaints related to the horseshoe kidney, cardiovascular risk factors (hypertension, diabetes mellitus, nicotine abuse and previous cardiovascular disease), diagnostic procedures used, diameter and extent of the aneurysm, presentation (asymptomatic or ruptured), time of diagnosis of the horseshoe kidney (preoperative or peroperative), and the general and vascular anatomy of the horseshoe kidney. Data were also collected about the operative approach, the level of cross-clamping of the aorta, separation of the isthmus, and the number of renal arteries arising from the aneurysm and how these were handled during operation. Follow-up time was recorded, as well as the postoperative serum creatinine level, morbidity and mortality. Cases were analysed according to clinical presentation (asymptomatic or ruptured). The influence of the time of diagnosis (preoperative *versus* peroperative) of the horseshoe kidney was analysed for both groups.

Results

Patients

A total of 176 cases was reported in the 88 articles published from 16 countries between 1956 and 1999[3–90] (including the authors' own two cases). One case report described the combination of an aortic aneurysm with a cake kidney[47], a form of fusion of the kidneys in which both the upper poles and the lower poles are fused; this case was included in the study. Information on the follow-up time and the postoperative serum creatinine level was described for less then 15 per cent of the patients, so these variables were excluded from the analysis. There were 148 men and 11 women; the sex was not reported for the remaining 17 patients. Mean age was 65 (range 31–91) years. Seventy patients (40 per cent) were reported to have cardiovascular risk factors. Of these, 38 had hypertension, ten diabetes mellitus, 28 nicotine abuse and 35 had a history of cardiovascular disease. Seven patients (4 per cent) had complaints related to the horseshoe kidney; two were caused by hydronephrosis, four by kidney stones and one patient had recurrent infections in combination with kidney stones. Almost all (172; 98 per cent) of the horseshoe kidneys had a parenchymatous isthmus; a fibrous isthmus was recorded in three and in one the anatomy was not reported. In 134 patients (76 per cent) the aneurysm was asymptomatic. Acute presentation with a ruptured aneurysm occurred in 42 cases (24 per cent).

Asymptomatic aneurysms

In this group of 134 aneurysms[4–6,8–15,17–26,28,30,32–35,37,39,40,43,44,46,48–51,53,57,61–64,66–70,72,73,75,76,78–84,86–90] the aneurysm was diagnosed by abdominal radiography in 11 cases (8 per cent), aortography in 41 (31 per cent) and ultrasonography in 16 cases (12 per cent). Computed tomography (CT) was used as a diagnostic procedure in 51 patients (38 per cent). In two instances the aneurysm was an operative finding and in one patient diagnostic laparoscopy, performed on the suspicion of appendicitis, revealed the abdominal aneurysm and a horseshoe kidney. In 12 patients (9 per cent) the modality used to diagnose the aneurysm was not described. There were 77 aneurysms of the abdominal aorta (57 per cent) and 53 aortoiliac aneurysms (40 per cent); in four instances (3 per cent) the extent of the aneurysm was not reported. Mean diameter was 68 (range 30–110) mm but in 57 cases the diameter was not recorded. Most horseshoe kidneys (108; 81 per cent) were diagnosed before operation; 26 were diagnosed during surgery. In these 26 cases the aneurysm had been diagnosed by plain abdominal radiography in three, by aortography in seven and by ultrasonography in nine cases. In two cases CT had been used and the horseshoe kidney had been missed. The diagnostic procedure was not described for the remaining five patients.

Table 1 shows the vascular anatomy and the number of renal arteries occluded and re-anastomosed for the horseshoe kidneys diagnosed before and during operation in both the asymptomatic and ruptured groups. The mean number of renal arteries in the asymptomatic group was 3·1 (range 2–7) and 3·9 (range 2–16) for the horseshoe kidneys diagnosed before and during operation respectively. *Table 2* shows the same variables for the six different operative approaches described: transperitoneal approach without separation of the renal isthmus (84 cases)[4,10,12–15,17–19,21–23,26,28,30,32,33,35,37,39,43,44,46,48–50,53,61,62,64,66–68,70,72,73,76,78,80,82,86,87,89], transperitoneal approach with separation of the renal isthmus (31)[5,6,9,17,20,23–25,34,39,40,46,49–51,53,57,62–64,67,79,80,86], retroperitoneal approach (ten)[17,

Table 1 Renal arteries: anatomy and management

	Asymptomatic aneurysms Horseshoe kidney diagnosed		Ruptured aneurysms Horseshoe kidney diagnosed	
	Before operation	At operation	Before operation	At operation
No. of cases	108	26	23	19
Cases with renal arteries originating from aneurysm	42	12	10	9
Total no. of renal arteries	325	102	78	53
From aneurysm	77	>30	18	13
Occluded*	34	13	16	7
Re-anastomosed*	34	11	2	6

*Arteries originating from aneurysm

[69,70,75,78,81,83,84], placement of a stent-graft (three)[88,90], polyester wrap (two)[8,57] and exploration without exclusion of the aneurysm (four)[3,8,11,35]. Aortic cross-clamping above the level of the renal arteries was performed in five cases (4 per cent). In 11 (8 per cent) the clamp was applied below the renal arteries and in four (3 per cent) it was positioned between the renal arteries. The level of cross-clamping of the aorta was not described in 114 cases (85 per cent). Complications were reported in nine patients (7 per cent). Two developed ischaemia of one leg, treated by embolectomy. Two had postoperative bleeding requiring re-exploration; one of these patients had developed a retroperitoneal haematoma caused by bleeding from the cut edges of a separated renal isthmus. Five patients (4 per cent) developed renal insufficiency, of whom three needed temporary haemodialysis. Division of renal arteries was described in two of the five cases complicated by renal insufficiency; in none of these cases was the level of cross-clamping of the aorta mentioned. Of the five patients who suffered from renal insufficiency, four had had a transperitoneal approach to the aneurysm with separation of the renal isthmus and the remaining patient had had a transperitoneal approach without separation of the renal isthmus. Five (4 per cent) of the patients with an asymptomatic aneurysm died, two from haemorrhagic shock, two from multiorgan failure and one from renal insufficiency.

Ruptured aneurysms

In this group of 42 aneurysms[7,16,27,29,31,36,38,41,42,44–47,49,50,52,54–56,58–60,62,64,65,67,71,74,77,78,85,86] the aneurysm was diagnosed by physical examination in 18 instances. In one patient a plain abdominal radiograph was the diagnostic procedure used. Eleven aneurysms were diagnosed by aortography, six by ultrasonography and five by CT. In one case the diagnostic procedure used was not described. A thoracoabdominal aneurysm was diagnosed in one patient. In 20 patients the aneurysm was limited to the abdominal aorta and in 21 there was iliac involvement. The diameter of the aortic aneurysms varied from 30 to 250 (mean 86) mm; the diameter was not described in 26 cases. The horseshoe kidney was diagnosed before operation in 23 patients and during operation in 19 patients (*Table 1*). Of the 19 patients in whom the horseshoe kidney was diagnosed during operation, the aneurysm had been diagnosed by physical examination in 15, by abdominal radiography in one and by aortography in two patients. In one case the method of diagnosis of the aneurysm was not described.

The mean number of renal arteries was 3·3 (range 2–7) and 2·7 (range 1–7) for horseshoe kidneys diagnosed before and after operation respectively. *Table 3* shows the vascular anatomy and the number of renal arteries occluded and re-anastomosed for the three operative approaches described in this group: transperitoneal approach without separation of the renal isthmus (21 cases)[27,29,36,38,44,47,49,50,56,62,64,67,71,74,77,78,86], transperitoneal approach with separation of the renal isthmus (20)[16,29,31,41,42,45,46,49,50,52,54,55,58–60,62,64,65,67,71,86] and placement of a stent-graft (one)[85]. In five cases the aorta was cross-clamped above the level of the renal arteries, in seven the aortic clamp was applied below the level of the renal arteries and in the remaining 30 cases the level of cross-clamping was not described. Eight patients developed complications. Ischaemia of one leg, requiring embolectomy, was noted in one patient. Development of renal insufficiency was described in seven patients, four of whom were treated with temporary haemodialysis. One of the seven cases complicated by renal insufficiency had had suprarenal aortic cross-clamping; the level of cross-clamping was not reported for the other six. Division of renal arteries originating from the aneurysm was not described in any of the seven cases complicated by renal insufficiency. Of these seven cases, renal insufficiency occurred after a transperitoneal approach with separation

Table 2 Renal arteries: operative intervention and management in the elective setting

	Transperitoneal approach						
	No separation of renal isthmus	Separation of renal isthmus	Retroperitoneal approach	Stent-graft	Wrap	Exploration†	Total
No. of cases	84	31	10	3	2	4	134
Cases with renal arteries originating from aneurysm	28	18	2	2	1	3	54
Total no. of renal arteries	252	99	41	12	3	20	427
From aneurysm	47	35	7	3	2	>13	>107
Occluded*	17	20	7	3	0	n.a.	47
Re-anastomosed*	30	15	0	n.a.	n.a.	n.a.	45

*Arteries originating from aneurysm. †Exploration without exclusion of the aneurysm. n.a., Not applicable

Table 3 Renal arteries: operative intervention and management in the emergency (ruptured aneurysm) setting

	Transperitoneal approach			
	No separation of renal isthmus	Separation of renal isthmus	Stent-graft	Total
No. of cases	21	20	1	42
Cases with renal arteries originating from aneurysm	6	12	1	19
Total no. of renal arteries	57	70	4	131
From aneurysm	11	19	1	31
Occluded*	9	13	1	23
Re-anastomosed*	2	6	n.a.	8

*Arteries originating from aneurysm. n.a., Not applicable

of the renal isthmus in three. Six patients in this group died, three from haemorrhagic shock, one from multiorgan failure, one from adult respiratory distress syndrome and one from myocardial infarction.

Discussion

The first documentation of a horseshoe kidney was by Berenger de Carpi in 1522[92], but the first detailed description of the anomaly was written in 1665 by Botallus[93]. The combination of a horseshoe kidney and an abdominal aortic aneurysm was described for the first time by Julian in 1956[3], and in 1957 Phelan *et al.*[4] were the first to exclude an aneurysm in the presence of a horseshoe kidney. Since that time a number of operative approaches have been described to enable the aneurysm to be repaired with preservation of renal function. At first, exclusion of the aneurysm was considered to be too difficult because of the complex vascular anatomy (years of publication 1956, 1964, 1968 and 1975)[3,8,11,35]; two reports describe the aneurysm being wrapped with polyester, a therapy now obsolete (years of publication 1964 and 1984)[8,57]. In the early years when aneurysms were excluded, the renal isthmus overlying the aorta was divided (years of publication between 1959 and 1997, median 1980)[5,6,9,16,17,20,23–25,29,31,34,39–42,45,46,49–55,57–60,62–65,67,71,79,80,86], but the need to divide the isthmus gradually disappeared with increasing operative experience (years of publication between 1957 and 1999, median 1986)[4, 10, 12–15, 17–19, 21–23, 26–30, 32, 33, 35–39, 43, 44, 46–50,53,56,61,62,64,66–68,70–74,76–78,80,82,86,87,89]. In later years a retroperitoneal approach to the aneurysm was advocated by some authors (years of publication between 1969 and 1997, median 1993)[17,69,70,75,78,81,83,84] and, finally, the endoluminal placement of a stent-graft was introduced as a method of treating selected cases of aneurysm plus horseshoe kidney (years of publication 1997, 1998 and 1999)[85,88,90].

The incidence of horseshoe kidney is between 1 : 600 and 1 : 800; it is twice as common in men as in women[1]. Because men have a higher incidence of aortic aneurysm[94], the combination of a horseshoe kidney and aneurysm is encountered more frequently in men, as the present study has shown. Nevertheless the male : female ratio in the present work of about 13 : 1 is higher than might be expected. Numerous cardiovascular anomalies have been reported to accompany horseshoe kidney[95–97], and so those with such a lesion might be at higher risk of developing an aortic aneurysm than the general population. Two-thirds of horseshoe kidneys present as complications, such as recurrent urinary tract infection, renal calculi and hydronephrosis[1]. In this review, only seven patients (4 per cent) were reported to have one of these complications. Presumably more patients must have had such complaints, but they were not described in the publications studied. The same holds for cardiovascular risk factors which were reported in only 70 cases (40 per cent).

CT provides the best chance of diagnosing both the abdominal aneurysm and the horseshoe kidney (*Fig. 1*), followed by aortography (*Fig. 2*). The horseshoe kidney was missed on CT in only two cases and in 17 per cent of the aortographies. Because CT is now the initial diagnostic modality of choice for asymptomatic aortic aneurysms[98], the presence of a horseshoe kidney will often be known before operation. As would be expected, the chance of an unanticipated horseshoe kidney is far greater in those with a ruptured aneurysm than in the elective setting. In the group with ruptured aneurysm, the renal anomaly was diagnosed during operation in 19 of 42 patients (45 per cent); in the asymptomatic aneurysm group the proportion was 19 per cent. This difference is caused by the lack of time for diagnostic tests in the emergency setting. For asymptomatic aneurysm, an equal number of renal arteries arising from the aneurysm was occluded (51 per cent) or re-anastomosed (49 per cent) on the graft, independent of the time of diagnosis

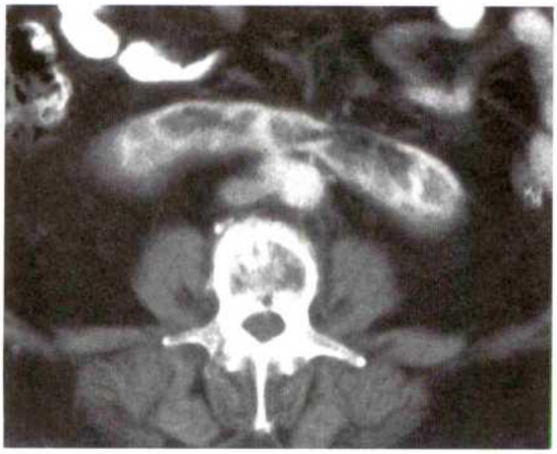

Fig. 1 Computed tomography showing the parenchymatous isthmus of a horseshoe kidney overlying the non-dilated part of the aorta just proximal to an aortic aneurysm

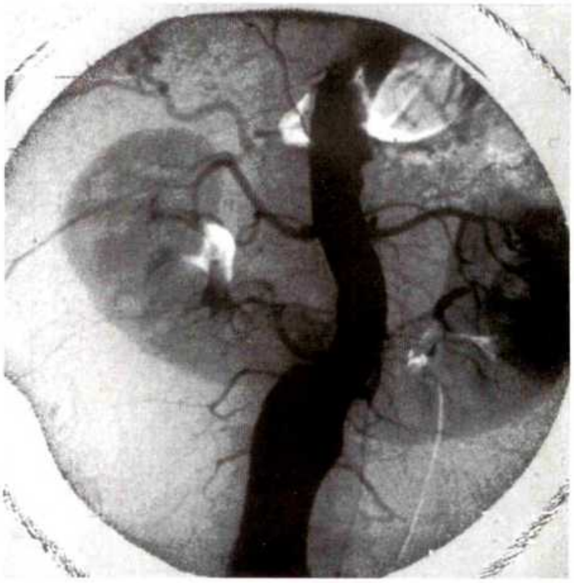

Fig. 2 Aortography of the patient in *Fig. 1* showing an aortic aneurysm and a horseshoe kidney. There are two renal arteries on the left side and two on the right side; all four arteries originate from the aorta above the level of the aneurysm

of the horseshoe kidney. For ruptured aneurysms, the majority of the renal arteries arising from the aneurysm were occluded (23 of 31). There does not seem to be any advantage of a preoperatively diagnosed horseshoe kidney in this group, as the proportion of divided renal arteries was highest in the preoperatively diagnosed group (16 of 18 compared with seven of 13 in the peroperatively diagnosed horseshoe kidneys). However, it should be noted that most of the renal arteries that were divided were described as being small.

In the majority of patients, the aneurysm was excluded through a transperitoneal approach, with or without separation of the renal isthmus. A transperitoneal approach without division of the renal isthmus (*Fig. 3*) was reported in 63 per cent of the asymptomatic group and in 50 per cent (21 of 42) of the ruptured group. A transperitoneal approach with separation of the renal isthmus was performed in 23 per cent of the asymptomatic group and in 48 per cent (20 of 42) of the ruptured group. In the asymptomatic patients more renal arteries arising from the aneurysm were divided when the isthmus was split than when it was left intact. This result was to be expected because the arteries to the renal isthmus have a higher chance of being divided when the horseshoe kidney is split. For ruptured aneurysm, the need for rapid vascular control probably lowers the threshold for division of the renal arteries and isthmus. This may well be the reason for the high proportion of divided renal arteries and isthmuses in the emergency setting.

Although transperitoneal exposure for aortic reconstruction has been dominant over the past four decades[99], some authors advocate a retroperitoneal approach for aortic surgery[78,100,101]. This has several advantages over the transperitoneal approach. It avoids interference with the renal isthmus, the urethers and most renal arteries and veins. However, the approach to the contralateral iliac artery is more difficult and the technique has been used exclusively in the elective setting. The present review shows that, although said to be relatively easy, the renal arteries arising from the aneurysm were all divided and no anastomoses to the the aortic prostheses were made using the retroperitoneal approach. However, there were only ten cases, a number that is too small to permit any definite conclusion. The authors believe that the theory behind using a retroperitoneal approach for asymptomatic aortic aneurysm in combination with a horseshoe kidney is strong. Despite the fact that in all published series all renal arteries arising from the aorta were divided, the retroperitoneal method can be advocated in the elective setting.

Theoretically, the easiest method of avoiding the technical difficulties associated with the combination of an aortic aneurysm and a horseshoe kidney is to treat the aneurysm endoluminally with a stent-graft[88,102,103]. The disadvantage is that, for obvious reasons, aberrant renal arteries cannot be anastomosed to the prosthesis and will be covered by the stent-graft. If these vessels originate from the aneurysm neck, it would be possible to place a bare stent across their origins[85,88] but, as is shown in *Tables 2* and *3*, all renal arteries arising from the aneurysm were obliterated in both the asymptomatic and the ruptured cases using this method. A limitation of the technique is that the morphol-

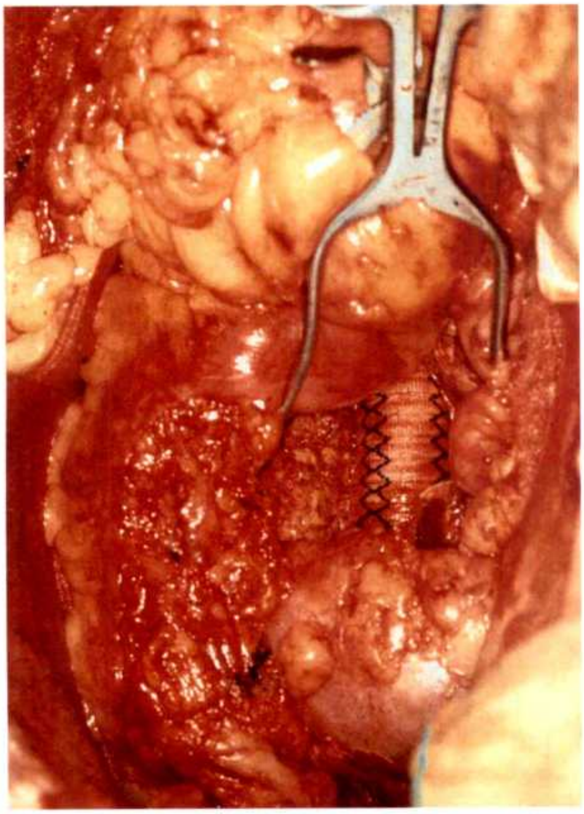

Fig. 3 Peroperative view of the patient in *Figs 1* and *2*. A horseshoe kidney lies inferior to a tube graft excluding an aortic aneurysm

ogy of the aneurysm must be suitable for endovascular exclusion. This, and the presence of many or large renal arteries originating from the aneurysm, creates a contraindication to stent-graft placement in most cases. In the authors' opinion, the endovascular exclusion of an asymptomatic aneurysm can be advocated when morphologically feasible, but it must be accepted that support for this statement is scant as only four cases have so far been reported.

Complications were much less common in the asymptomatic patients than in those with ruptured aneurysm (7 per cent and 19 per cent (eight of 42) respectively). Renal insufficiency was the most common complication in both groups (4 per cent and 17 per cent (seven of 42) respectively). Division of the renal isthmus seems to increase the chance of developing renal insufficiency in both the elective (four of 31 cases) and emergency (three of 20) setting. Unfortunately, the level of aortic cross-clamping was described very infrequently and so no conclusion about suprarenal aortic cross-clamping in relation to renal insufficiency can be drawn. Surprisingly, the number of renal arteries originating from the aneurysm that are divided does not seem to influence postoperative renal function. The most probable explanation is that the divided arteries were small. One patient with an asymptomatic aneurysm suffered a haemorrhage after division of the renal isthmus. Together with urinary fistula formation, this is a frequently described complication of splitting the isthmus[104]. These findings suggest that the renal isthmus should ideally be left intact to reduce morbidity. In patients in whom the aneurysm was approached retroperitoneally or in whom a stent-graft was placed, no morbidity or death was reported.

The authors recognize that this study is biased because of an under-reporting of failed cases. This is illustrated by the low mortality rate of 14 per cent (six of 42 patients) in the group with ruptured aneurysm. Nevertheless, this review presents the most complete data set possible; it can be used to suggest the optimal treatment and the pitfalls in handling the combination of an aortic aneurysm and a horseshoe kidney. Certainly, not treating the aneurysm, as described in some early cases[3,8,11,35,57,71], can no longer be advocated in view of modern therapeutic possibilities.

Recommendations

A guideline for the diagnosis and treatment of aortic aneurysm in combination with a horseshoe kidney is outlined in *Fig. 4*. Adequate preoperative diagnosis of the horseshoe kidney and its vascular anatomy is important in choosing the best surgical approach in each individual patient, even though it does not seem to influence the peroperative handling of aberrant renal arteries. The unanticipated combination of an aneurysm and a horseshoe kidney can be avoided by using helical CT which is, in any event, the diagnostic modality of choice for general planning of surgery for aortic aneurysm. If helical CT is not available, the combination of conventional CT and aortography is advised. When a patient with a ruptured aneurysm is in shock there is no time for extensive diagnostics. In such cases the aneursym is diagnosed by physical examination and ultrasonography, and the presence of a horseshoe kidney might be missed. However, this has no significance in the choice of surgical approach. In the emergency setting the authors advocate a transperitoneal approach to gain maximal overview and rapid vascular control. Clamping of the aorta can be done at the usual site. The risk of damage to the horseshoe kidney and its vasculature is minimal because of the distal position of the organ and the fact that most abberant renal arteries originate distal to the horseshoe kidney itself. The renal isthmus should be spared if possible. In patients with an asymptomatic aneurysm, the horseshoe kidney should normally be discovered before operation. Adequate know-

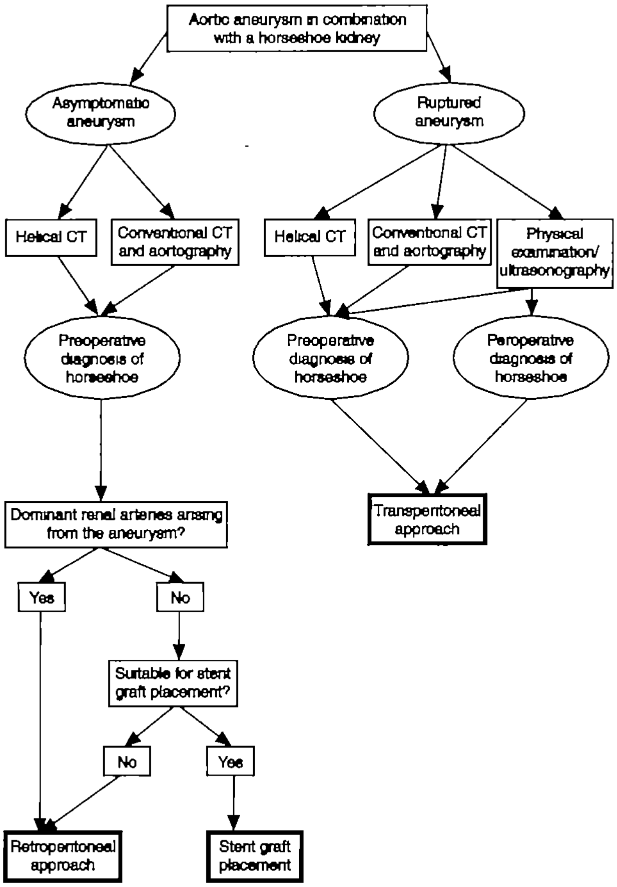
Aortic aneurysm in combination with a horseshoe kidney
Asymptomatic aneurysm
Ruptured aneurysm
Helical CT
Conventional CT and aortography
Helical CT
Conventional CT and aortography
Physical examination/ ultrasonography
Preoperative diagnosis of horseshoe
Preoperative diagnosis of horseshoe
Peroperative diagnosis of horseshoe
Dominant renal arteries arising from the aneurysm?
Transperitoneal approach
Yes
No
Suitable for stent graft placement?
No
Yes
Retroperitoneal approach
Stent graft placement

Fig. 4 Flow diagram showing the diagnosis and treatment of aortic aneurysm in combination with a horseshoe kidney. CT, computed tomography

ledge of the vascular anatomy is essential to determine the approach of choice in such circumstances. When the aortic morphology is suitable and no dominant renal arteries originate from the aneurysm, the placement of a stent-graft should be considered. If dominant renal arteries arise from the aneurysm, the retroperitoneal approach seems to be a valuable method which avoids the overlying isthmus. As many accessory renal arteries as possible should be re-anastomosed to the prosthesis.

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Single-blind randomized clinical trial of laparoscopic *versus* open appendicectomy in children

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Background: Appendicectomy is the most common emergency surgical operation in children. The aim of this study was to compare recovery after appendicectomy using either a laparoscopic or an open technique in children.

Methods: Sixty-one children aged 4–15 years undergoing appendicectomy for suspected uncomplicated appendicitis were studied. The study was prospective, randomized and single-blinded, with parallel groups. Standardized anaesthetic technique and pain management were used. The study endpoints were postoperative pain, need for rescue analgesia, and length of hospital stay.

Results: Children had significantly less pain after laparoscopic compared with open appendicectomy 8 h after operation and on the first and second postoperative mornings ($P < 0{\cdot}05$). Laparoscopic appendicectomy resulted in a reduced requirement for rescue analgesia with oxycodone in hospital: mean(s.d.) 3·6(2·5) *versus* 5·8(3·3) doses (mean difference 2·2 doses, 95 per cent confidence interval (c.i.) 0·6–3·8 doses); $P = 0{\cdot}01$. The mean(s.d.) length of hospital stay was significantly shorter in the laparoscopic group: 1·9(0·7) *versus* 2·6(0·9) days (mean difference 0·7 days, 95 per cent c.i. 0·3–1·1 days); $P = 0{\cdot}001$. Three children who had open appendicectomy developed a wound infection.

Conclusion: Laparoscopic appendicectomy is associated with less postoperative pain and a shorter hospital stay than open appendicectomy in children undergoing surgery for uncomplicated appendicitis.

Paper accepted 3 November 2000

British Journal of Surgery 2001, 88, 510–514

Introduction

Acute appendicitis is the most common indication for emergency surgery among children[1]. Appendicectomy has been the 'treatment of choice' for appendicitis for nearly a century. Although it is a simple operation associated with a very low mortality rate, appendicectomy may result in significant postoperative morbidity, particularly postoperative pain[2,3]. Laparoscopic appendicectomy was first described in 1983 and has since become routine in many centres[4]. Laparoscopic surgery is expected to offer potential benefits because it is a less traumatic surgical technique[1]. However, the benefits of laparoscopic appendicectomy remain unproven. One study in children showed that the laparoscopic approach allows a faster recovery after operation[5], but another found no advantage compared with open surgery[3]. The present study was designed to address these conflicting findings.

This study was undertaken to evaluate recovery after laparoscopic appendicectomy compared with open appendicectomy in children with suspected uncomplicated appendicitis. Children with complicated disease were not included in the final analysis. It is known that advanced appendicitis with peritonitis is associated with prolonged hospital stay, irrespective of the surgical approach[6]. The study variables were pain after operation, the need for rescue analgesia, and length of hospital stay. Recovery at home was evaluated, comparing severity and duration of pain and the need for analgesia after operation.

Patients and methods

The study was approved by the ethics committee of Kuopio University Hospital and Kuopio University, and was conducted in accordance with the Declaration of Helsinki. Children who were old enough and parents gave written informed consent. Seventy-three children (31 girls), with American Society of Anesthesiologists physical status I or II, aged 4–15 years, 15–75 kg in weight, undergoing emergency appendicectomy between November 1997 and

November 1999 were studied. Children who had had previous abdominal operations and those with a known allergy to ketoprofen or other non-steroidal anti-inflammatory drugs, asthma, kidney or liver dysfunction, haemorrhagic diathesis, or neurological disease were excluded.

The study design was prospective, randomized and single-blinded, with parallel groups. The diagnosis of acute appendicitis was based on a history of abdominal pain and persistent right lower quadrant tenderness. After a decision to operate, patients were allocated randomly (a sealed envelope method) to undergo either laparoscopic or open appendicectomy. Children, parents, research nurses and paediatric surgeons, except the principal investigator (H.L.), were blinded with respect to whether the patient was operated on via a laparoscopic or open technique, and remained blinded until a control visit scheduled for 7 days after operation.

After operation each child had a similar wound dressing (*Fig. 1*). At discharge only five of 16 children, three of 14 parents and five of 16 nurses were able to guess correctly the type of operation performed, with a similar distribution between the study groups. Five children, six parents and six nurses gave a wrong guess, and six children, five parents and five nurses were not able to give any answer.

A standard orotracheal anaesthetic technique was used. Children were premedicated with diazepam orally. Fentanyl 2 µg/kg was given intravenously and anaesthesia induced with thiopental; neuromuscular block was achieved with *cis*-atracurium. Anaesthesia was maintained with sevoflurane in oxygen 35 per cent in air with intermittent positive pressure ventilation. No local anaesthetics were used. All children had a nasogastric tube during the operation, and metronidazole 7 mg/kg was given intravenously at induction as antibiotic prophylaxis.

Laparoscopic procedures were performed by one paediatric surgeon (H.L.) with experience of more than 30 laparoscopic appendicectomies. Patients in the open appendicectomy group were operated on by 13 surgeons, all of whom had experience of more than 200 open appendicectomies.

Laparoscopic appendicectomy was performed in a standardized manner using two 5-mm working ports and one 5- or 10-mm sheath for the camera. A pneumoperitoneum was created with the pressure maintained below 12 mmHg. If a normal appendix was encountered, the entire abdominal cavity was explored laparoscopically. Open appendicectomy was performed through a McBurney incision. Operating time (from skin incision to wound closure) and total procedure time (from the time the patient arrived in the operating room until admission to the postanaesthesia care unit) were recorded.

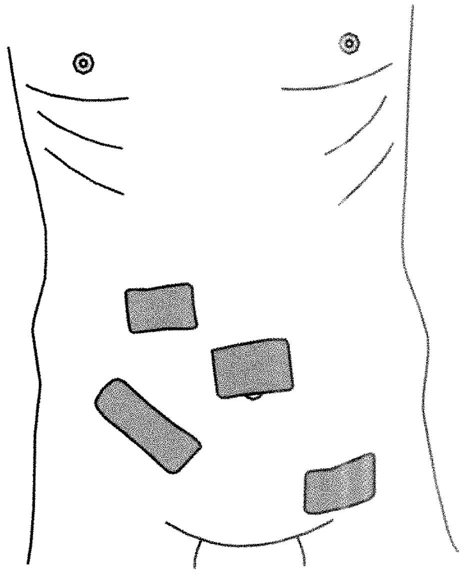

Fig. 1 Schematic representation of the wound dressing used for each child after appendicectomy to allow blinding

After operation postoperative pain was first assessed using the Maunuksela pain score (0, no pain; 10, worst possible pain) by specially trained research nurses, and thereafter children were asked to express the pain on a visual analogue scale. Pain scores were recorded at rest and on coughing.

On completion of the operation each child was given ketoprofen 1 mg/kg as an intravenous bolus followed by 4 mg/kg over 24 h for background analgesia. After 24 h, pain treatment was continued with ketoprofen tablets (5 mg/kg over 24 h). If the child was in pain (pain score of 3 or more at rest, or 5 or more on coughing), oxycodone 0·05 mg/kg intravenously or 0·1 mg/kg transmucosally was given for rescue analgesia. Oxycodone was repeated at 15-min intervals until the child was comfortable. The number of oxycodone doses was recorded. No other analgesic treatment was permitted during the study. All adverse events were recorded for each child.

Children were discharged when they could tolerate a normal oral diet, had no dizziness or vomiting, were able to walk straight, had been apyrexial for 12 h (temperature lower than 37·5°C), had no difficulty in passing urine, and had only mild pain, which was treated with oral ketoprofen.

Recovery at home was evaluated by means of a diary for the first 7 days and by a follow-up call 4 weeks after operation. At home, pain was assessed using a four-point verbal rating scale (0, no pain; 3, severe pain). The diary was returned, the surgical dressings were removed and the blinding was opened at the control visit 7 days after the operation.

Statistical analysis

A power analysis suggested that, to have an 80 per cent chance of obtaining a 35 per cent reduction in the need for rescue analgesia at an α level of 0·05, a minimum of 30 children per group would be needed.

Analysis of continuous variables was performed using a two-tailed *t* test for two independent samples. For categorical variables the χ^2 test and Fisher's exact test were used. $P \leq 0 \cdot 05$ was considered statistically significant. Results are presented as the number of cases, mean(s.d.), mean difference and 95 per cent confidence intervals (c.i.) as appropriate.

Results

Patients

Thirty-six children underwent open appendicectomy and 37 had laparoscopic appendicectomy. Twelve children, five in the open group and seven in the laparoscopic group, had either local or diffuse peritonitis and so were excluded from the evaluation, thus leaving 31 children in the open group and 30 in the laparoscopic group. The two groups were similar in terms of age, weight, height and surgical diagnosis (*Table 1*).

Surgery

There was no need for conversion from laparoscopic to open appendicectomy. The mean(s.d.) operating time was similar in the two groups (34(18) min in the laparoscopic group and 30(11) min in the open group), but the total procedure time was significantly longer in the laparoscopic group (82(26) *versus* 62(15) min (mean difference 20 min, 95 per cent c.i. 9–31 min); $P = 0 \cdot 001$).

Postoperative pain

The pain scores were lower in the laparoscopic group. The difference between the two groups was significant 8 h after operation and on the first and second mornings after operation (*Fig. 2*).

Table 1 Patient characteristics

	Laparoscopic ($n = 30$)	Open ($n = 31$)
Sex ratio (F : M)	10 : 20	16 : 15
Weight (kg)*	44(16)	46(14)
Height (cm)*	150(18)	152(17)
Age (years)*	11(3)	12(3)
Appendix (normal : acute appendicitis)	8 : 22	11 : 20

*Values are mean(s.d.)

No patient in the open group experienced shoulder pain, compared with six children in the laparoscopic group. In these six children the shoulder pain lasted for a mean(s.d.) of 14(9) (range 2–29) h.

Every child in the open group and 28 of the 30 children in the laparoscopic group received rescue analgesics. In the laparoscopic group 15 children received two or fewer doses of oxycodone, compared with only three of the 31 children in the open group ($P = 0 \cdot 001$, χ^2 test). Overall, the requirement for oxycodone was significantly lower in the laparoscopic than in the open group (*Table 2*).

Adverse effects

No patient vomited in the postanaesthesia care unit and only one child in each group experienced nausea. On the ward four children in the laparoscopic group and three in the open group vomited. One child in the laparoscopic group had urinary retention requiring bladder catheterization. Three children in the open group developed a wound infection.

Discharge

The mean(s.d.) length of hospital stay was significantly shorter in the laparoscopic group (1·9(0·7) *versus* 2·6(0·9) days (mean difference 0·7 days, 95 per cent c.i. 0·3–1·1 days); $P = 0 \cdot 001$). Hospitalization of 3 days or more was required for five children in the laparoscopic group,

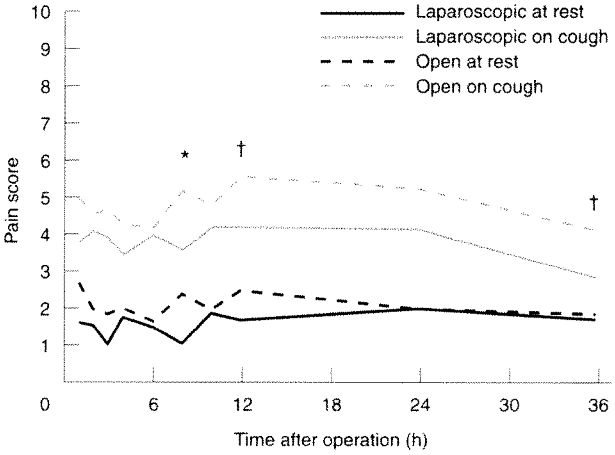

Fig. 2 Mean pain scores after laparoscopic or open appendicectomy determined by a pain scale: 0, no pain; 10, worst possible pain. $^*P < 0 \cdot 05$ between the two groups at rest; $^\dagger P < 0 \cdot 05$ between the two groups at cough (analysis of variance)

Table 2 Need for rescue analgesics in the two study groups

	Laparoscopic ($n=30$)	Open ($n=31$)	Mean difference†	P‡
No. of oxycodone doses*				
In PACU	1·5(1·5) (0–6)	3·0(1·9) (0–8)	1·5 (0·6–2·4)	0·001
5–24 h	1·6(1·6) (0–5)	2·2(1·6) (0–6)	0·6 (–0·2–1·4)	0·11
25–48 h	0·2(0·4) (0–1)	0·6(1·2) (0–6)	0·3 (–0·1–0·9)	0·15
Total	3·6(2·5) (0–9)	5·8(3·3) (1–16)	2·2 (0·6–3·8)	0·01
Total oxycodone dose (mg/kg)*	0·23(0·19) (0–0·6)	0·36(0·23) (0·04–1·2)	0·13 (0·02–0·24)	0·01

*Values are mean(s.d.) (range); †values in parentheses are 95 per cent confidence intervals. PACU, postanaesthesia care unit. ‡Mann–Whitney *U* test

compared with 16 children in the open group (difference 35 per cent, 95 per cent c.i. 13–57 per cent; $P = 0{\cdot}004$, χ^2 test).

Recovery at home

Fifty-eight diaries (95 per cent) were returned. All children experienced pain at home, and ten children in the laparoscopic group and 11 in the open group experienced the highest pain scores (moderate or severe). At home, children in the laparoscopic group received fewer analgesic doses and had pain for a shorter duration compared with children in the open group, but the differences were not significant.

At 1 week after operation, four children in laparoscopic group experienced some degree of pain, compared with 11 in the open group ($P = 0{\cdot}05$, χ^2 test). No patient in the laparoscopic group experienced significant pain, compared with three children in the open group ($P = 0{\cdot}24$, Fisher's exact test). At 4 weeks only one child in the open group experienced mild pain.

Discussion

In this study the recovery after laparoscopic appendicectomy was significantly improved compared with that following open appendicectomy. Children who underwent laparoscopic surgery had less pain and needed less rescue analgesia after operation than children who underwent open surgery. Moreover, the length of hospitalization was shorter after laparoscopic surgery. The duration of operations was similar with both techniques, but the preoperative installation of the videoendoscopic equipment took up to 20 min, thus increasing the total procedure time in the laparoscopic group.

The cost-effectiveness of laparoscopic technique is difficult to determine. It depends on the balance between excess operating costs and decreased hospital stay. In this study the same reusable instruments were used to reduce the costs of laparoscopic appendicectomy. Disposable equipment included endoloop ties (two per procedure) and suture materials. The total procedure time was longer, thus increasing operating room costs. Length of hospitalization was, however, decreased for patients having laparoscopic appendicectomy, resulting in an overall reduction in hospital costs.

Lejus *et al.*[3] conducted a randomized blinded study that compared laparoscopic with open appendicectomy in children, but did not find any difference in pain or recovery after operation. In contrast with the present study, they also included patients with complicated appendicitis. There is a wide range of clinical presentations in children with acute appendicitis. Patients with more complex disease have more complications regardless of the surgical approach[7–9]. In the present study children with complicated appendicitis were excluded and only those with uncomplicated appendicitis or a normal appendix were evaluated. In a previous study Hay[5] compared these two surgical approaches and found recovery to be superior after laparoscopic surgery. However, in that study randomization was based on parental consent and the study was not blinded.

Patient-controlled analgesia (PCA) is an effective technique of providing analgesia after operation. However, education of patients, parents and nurses is essential for its successful and safe use[2,10]. Because of limited experience with PCA in the authors' paediatric ward, it was decided to employ the normal postoperative pain treatment protocol which allows nurses to give opioids intravenously. However, pain treatment after appendicectomy remains a challenge whichever pain treatment is used. Morton and O'Brien[2] described a study in which all children received morphine before surgical incision and all had wound infiltration with bupivacaine at the end of the operation. Despite additional postoperative analgesia with PCA morphine, a significant proportion of children still experienced severe pain.

In the present study appendicectomy also resulted in significant pain: all except two children needed rescue analgesia despite background pain treatment with ketoprofen. However, pain after open surgery was more severe and lasted longer than with laparoscopic surgery. Ketoprofen has been shown to be an effective non-opioid analgesic in children after both minor and major surgery. Other studies have indicated that ketoprofen reduces or even eliminates the need for opioids after operation. Moreover, after major surgery ketoprofen results in better pain relief and may even reduce some adverse effects of opioids, for example emesis and respiratory depression[11,12].

It is concluded that the laparoscopic technique has distinct advantages compared with open surgery in children undergoing surgery for uncomplicated appendicitis or with a normal appendix. After laparoscopic appendicectomy, children have less pain and hospital stay is shorter than following open appendicectomy.

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Original article

Prognostic factors and survival after hepatic resection for hepatocellular carcinoma without cirrhosis

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Background: Detailed follow-up of patients with chronic hepatitis has resulted in increased diagnosis of hepatocellular carcinoma (HCC) in patients without cirrhosis. Despite numerous studies on hepatic resection, the prognostic factors for intrahepatic recurrence and survival are not well known for patients with HCC without cirrhosis.

Methods: Among 349 patients with HCC treated in the past 13 years, cirrhosis was absent in 126 patients (36 per cent). Curative hepatic resection was carried out in 100 (79 per cent) of these patients. Risk factors for intrahepatic recurrence and prognostic factors for survival were evaluated by univariate and multivariate analyses.

Results: Postoperative morbidity and mortality rates were 22 and 3 per cent respectively. The 5- and 10-year disease-free and overall survival rates were 31 and 50 per cent, and 22 and 47 per cent respectively. Blood loss, surgical resection margin, intrahepatic metastasis, portal vein invasion and extent of hepatic resection were independently associated with overall survival. However, the only risk factors for intrahepatic recurrence were portal vein invasion and hepatitis C virus (HCV) infection. The former was related to early recurrence while the latter was related to later recurrence. The 5-year disease-free survival rate was 58 per cent in patients with hepatitis B virus infection while it was 6 per cent in patients with HCV infection ($P < 0{\cdot}001$).

Conclusion: In the treatment of HCC without cirrhosis, major hepatectomy is advocated to prevent early recurrence. Liver transplantation may be required for patients with HCV infection.

Paper accepted 20 November 2000

British Journal of Surgery 2001, 88, 515–522

Introduction

Despite recent advances in diagnostic methods for hepatocellular carcinoma (HCC), the prognosis is generally poor. Hepatic resection remains the mainstay of treatment of this tumour and provides the only consistent long-term survival. Although many investigators have reported the prognostic factors for survival or the risk factors for tumour recurrence after resection of HCC, almost all series have included patients with and without cirrhosis, or only patients with cirrhosis. Surgical results for HCC are uniformly poor in the presence of cirrhosis, irrespective of aetiology.

The incidence of HCC has been increasing not only in Japan but worldwide[1]. In particular, hepatitis C virus (HCV)-associated HCC is increasing year by year in Japan. In contrast to hepatitis B virus (HBV) infection, HCV infection often progresses to a chronic carrier state and finally cirrhosis of the liver. It has been thought that HCC develops in HCV-positive patients only when the liver has become cirrhotic[2,3]. Since the first reports by Herr *et al.*[4] and Theise *et al.*[5] in 1993, several groups have reported that HCC can develop in non-cirrhotic livers of HCV-positive patients[6–11].

Hepatic resection can be performed in the absence of underlying cirrhosis. However, intrahepatic recurrence after curative resection of HCC is still unacceptably high even in patients without cirrhosis. To improve the surgical outcome in such patients, it is of crucial importance to clarify the prognostic factors for survival and the risk factors for intrahepatic tumour recurrence. The aim of this study was to evaluate these problems in 100 consecutive patients treated in the past 13 years.

The Editors have satisfied themselves that all authors have contributed significantly to this publication

Patients and methods

Between April 1986 and June 1999, 349 patients with primary HCC were admitted. Of these, 254 patients underwent potentially curative hepatic resection. The definition of curative resection was described previously[12]. The resectability rate was 79 per cent for patients without cirrhosis and 69 per cent for those with cirrhosis. One hundred of these patients had no underlying cirrhosis of the liver and are the subject of this study. There were 87 men and 13 women of mean age 61 (range 36–78) years. Alcohol abuse was noted in 59 patients and a history of blood transfusion was confirmed in 30 patients. Thirty-three patients were positive for hepatitis B surface (HBs) antigen while 42 (51 per cent) of 83 patients were positive for HCV antibody. Intra-arterial injection of oil contrast lipiodol with or without chemotherapeutic agents had been performed in 38 patients before referral, although all had resectable HCCs at the time of angiography.

Preoperative investigations

Detailed liver function tests including indocyanine green (ICG) and bromosulfophthalein tests were performed routinely (*Table 1*). Radioimmunoassay or enzyme immunoassay methods were used for detection of HBs antigen (IMxHBsAg-Dainapack; Dianabot, Osaka, Japan), anti-hepatitis B surface (anti-HBs), anti-hepatitis B core (anti-HBc), anti-hepatitis B envelope (anti-HBe) (Abbott Laboratories, Chicago, Illinois, USA). HCV antibody was measured by enzyme immunoassay methods (Ortho® HCV-Ab ELISA test; Ortho-Clinical Diagnostic, Rantan, New Jersey, USA). Serum α-fetoprotein (AFP) was estimated by a radioimmunoassay method. All patients had a 75-g oral glucose tolerance test to measure blood sugar and serum insulin concentrations. The diagnosis of diabetes mellitus was made on the basis of a fasting venous glucose level higher than 7·8 mmol/l or blood glucose concentration in excess of 11·1 mmol/l 2 h after ingestion of 75 g glucose. Ultrasonography, computed tomography (CT) and angiography were performed in all cases. Upper gastrointestinal barium studies and, when necessary, fibreoptic examination were performed routinely.

Hepatic resection

Extended right lobectomy was performed in 11 patients, right lobectomy in 27, extended left lobectomy in two, left lobectomy in seven, left lateral segmentectomy in six and other two-segment resection[13] in five patients. The remaining 42 patients underwent resection of one Couinaud's segment or less. For later analysis, the former 58 patients were assigned to the non-limited resection group and latter 42 patients to the limited hepatectomy group. The mean operation time was 148 (range 55–280) min. The mean blood loss during surgery was 913 (range 80–7000) ml.

Table 1 Preoperative laboratory data in 100 patients with hepatocellular carcinoma without cirrhosis

	Normal range	Patients with HCC
Albumin (g/dl)	3·8–5·1	3·9(0·5) (2·6–4·8)
Total bilirubin (mg/dl)	0·2–1·5	0·8(1·7) (0·2–17·2)
Aspartate aminotransferase (units/l)	5–40	61(44) (8–200)
Lactate dehydrogenase (units/l)	190–450	334(158) (132–1359)
Alkaline phosphatase (units/l)	21–80	146(157) (30–1002)
Cholinesterase (units/l)	210–540	396(366) (69–1466)
Prothrombin time (s)	11·0–14·0	11·8(1·0) (9·6–14·4)
ICG R15 (%)	<10	13·7(6·4) (4·5–33·8)
BSP R30 (%)	<5	19·1(8·3) (1·4–39·4)
Ammonia (μg/dl)	14–70	51(25) (20–150)
α-Fetoprotein (ng/ml)	<20	739(2962) (2–22 490)

Values are mean(s.d.) (range). HCC, hepatocellular carcinoma; ICG R15, indocyanine green retention rate at 15 min; BSP R30, bromsulphophthalein retention rate at 30 min

Histopathology

Histopathological features of the tumour surrounding liver were examined macroscopically and microscopically. The maximal diameter of the tumour was taken as the tumour size. The tumour node metastasis stage was decided according to the criteria of the American Joint Committee on Cancer[14]. Histological type and differentiation grade of the tumour were diagnosed by World Health Organization criteria[15]. The presence or absence of a hepatic capsule or portal vein invasion and intrahepatic metastasis (daughter nodules) was determined both macroscopically and microscopically. A surgical margin of less than 5 mm was defined as a positive margin. The criteria proposed by Anthony *et al.*[16] were used for the diagnosis of liver cirrhosis. Patients fulfilling this criteria were not included in the current analysis. The grade of hepatitis activity was assessed by Knodell's histology activity index[17]. The grade of liver fibrosis was determined by the criteria of Desmet *et al.*[18]. Detailed histopathological comparisons between hepatitis B and C cases were performed as described by Lefkowitch *et al.*[19].

Postoperative follow-up

Postoperative chemotherapy with epirubicin, 5-fluorouracil, and later mitomycin C and cisplatin was carried out on 54 patients in randomized studies. After discharge from hospital, the patients were followed up at 2-week intervals in the first 6 months and monthly thereafter. After 5 years, the follow-up interval was increased to 3 months. Imaging with ultrasonography and CT was repeated every 3 months. When tumour recurrence was suspected, the patient was hospitalized for further evaluation by angiography and, when necessary, magnetic resonance imaging. In equivocal cases, histological diagnosis was confirmed by echo-guided needle biopsy. Treatment methods for recurrence were decided by the recurrence pattern, hepatic functional reserve and patient's desire.

Statistical analysis

The endpoints were death and intrahepatic tumour recurrence. Non-parametric data were analysed by χ^2 test with Yates' correction. All patients were included for overall analyses but three postoperative deaths were excluded from disease-free survival analyses. Survival rates were obtained by the Kaplan–Meier method[20] and differences were compared by the log rank and generalized Wilcoxon tests. Univariate analysis was carried out by the χ^2 test. Multivariate analysis was performed by the Cox proportional hazards regression model using StatView 4.11® (Abacus Concepts, Berkeley, California, USA). Data were expressed as mean(s.d.) and as a hazard ratio with 95 per cent confidence intervals. All analyses were two tailed and $P < 0{\cdot}05$ was considered statistically significant.

Results

Preoperative associated conditions

The most commonly associated condition was diabetes mellitus which was found in 37 patients. Among these patients, 15 were positive for HCV antibody and ten were positive for HBs antigen. Other associated conditions were peptic ulcer in six patients, cholelithiasis in five, oesophageal varices in two and ascites in one.

Morbidity and mortality

Twenty-four complications occurred in 22 patients; pleural effusion in seven, bile leakage in four, pneumonia in two, gastrointestinal bleeding in two, acute pancreatitis in two, wound infection in two, postoperative bleeding in one, intestinal obstruction in one, pyloric stenosis in one, portal vein thrombosis in one and brain stem haemorrhage in one. Three patients (3 per cent) died after operation, on day 5 from brain stem haemorrhage, on day 23 from acute pancreatitis, and on day 24 from liver failure due to portal vein thrombosis. These patients were excluded from disease-free survival analysis.

Histopathological findings

Macroscopic and microscopic histopathological data of HCCs and the surrounding liver are summarized in *Table 2*. Although the grade of fibrosis was no different between hepatitis B and C, necroinflammatory activity was significantly greater in hepatitis C ($P < 0{\cdot}001$) (*Table 3*).

Table 2 Histopathological data of 100 cases of hepatocellular carcinoma in patients without cirrhosis

	Percentage of cases
Tumour size (cm)	
< 2·0	13
2·0–5·0	43
5·1–10·0	34
> 10·0	10
No. of tumours	
1	81
≥ 2	19
Stage (TNM)	
I	21
II	61
III	14
IV	4
Differentiation grade	
Well	21
Moderate	51
Poor	10
Undifferentiated	2
Unknown	16
Capsule present	71
Portal vein invasion	38
Intrahepatic metastasis	25
Positive surgical margin	32

TNM, tumour node metastasis

Table 3 Histological comparison of liver parenchyma between chronic hepatitis B and C

	HBV (n = 33)	HCV (n = 42)	P*
Liver fibrosis score			0·66
0	1	2	
1	18	19	
2	9	10	
3	5	11	
HAI score			< 0·001
1–3	0	0	
4–8	26	15	
9–12	7	27	
13–18	0	0	

HAI, hepatitis activity index[17]. *χ^2 test

Table 4 Clinical prognostic factors for disease-free and overall survival by univariate analysis

	Disease-free survival*			Overall survival		
	No. of patients	5-year survival (%)	*P*†	No. of patients	5-year survival (%)	*P*†
Age (years)			0·049			0·31
<50	12	71		12	69	
50–70	66	28		68	50	
>70	19	0		20	30	
HBs antigen			0·002			0·22
Positive	33	58		33	65	
Negative	64	14		67	39	
HCV antibody			0·007			0·55
Positive	41	6		42	39	
Negative	40	47		41	56	
Preoperative TAE			0·007			0·06
Yes	37	49		38	62	
No	60	17		62	41	
AST (units/l)			0·01			0·28
<100	83	36		85	53	
≥100	14	0		15	29	
BSP R30 (%)			0·003			0·27
<20	50	48		50	62	
≥20	47	12		48	35	
Extent of resection			0·37			0·015
Limited	42	33		42	63	
Non-limited	55	30		58	34	
Operative blood loss (g)			0·009			<0·001
<1000	69	33		72	56	
≥1000	28	25		28	32	

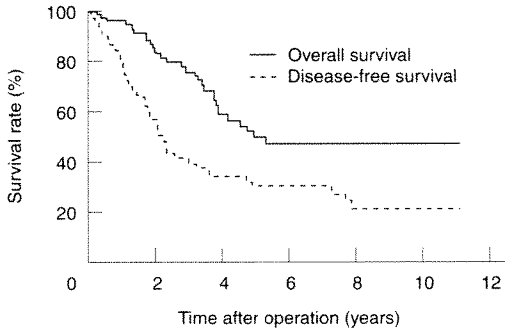
*Three postoperative deaths excluded. HBs, hepatitis B surface; HCV, hepatitis C virus; TAE, transcatheter arterial embolization; AST, aspartate aminotransferase; BSP R30, bromosulfophthalein retention rate at 30 min. †Log rank test

Intrahepatic tumour recurrence

Intrahepatic tumour recurrence was found in 50 patients. The mean recurrence-free period was 2·4 years (range 1 month to 11 years). The recurrence was solitary in 15 and multiple in 35 patients. Eight patients also had extrahepatic recurrences. One patient had only pulmonary metastases. Thus, 51 patients had tumour recurrence during follow-up. Intrahepatic recurrence was treated by repeat hepatectomy in 20 patients, transcatheter arterial chemoembolization (TAE) in 16 patients, intra-arterial or systemic chemotherapy in eight patients and percutaneous ethanol injection in six patients.

Survival

During follow-up (range 1 month to 11·6 years), 41 patients died, 31 from tumour recurrence, three from liver failure, two from complications after repeat hepatectomy, two from gastrointestinal bleeding, two from lung cancer and one from endocarditis. The overall 1-, 3-, 5- and 10-year survival rates were 97, 76, 50 and 47 per cent; the corresponding disease-free survival rates were 79, 38, 31 and 22 per cent respectively (*Fig. 1*).



No. at risk						
Overall survival	100	55	29	16	10	2
Disease-free survival	97	36	18	15	7	2

Fig. 1 Disease-free and overall survival rates after hepatic resection for hepatocellular carcinoma in patients without cirrhosis

Table 5 Histopathological prognostic factors for disease-free and overall survival by univariate analysis

	Disease-free survival*			Overall survival		
	No. of patients	5-year survival (%)	*P*†	No. of patients	5-year survival (%)	*P*†
Tumour size (cm)			0·07			0·1
<5	54	39		56	43	
⩾5	43	22		44	56	
No. of tumours			0·005			0·077
1	79	35		81	54	
⩾2	18	18		19	33	
Tumour stage (TNM)			0·05			0·01
I	20	58		21	78	
II	59	30		61	41	
III	14	32		14	39	
IV	4	75		4	75	
Tumour differentiation			<0·001			0·01
Well–moderate	69	28		72	53	
Poor–undifferentiated	12	11		12	44	
Portal vein invasion			0·03			0·01
Present	33	22		34	34	
Absent	53	34		55	55	
Intrahepatic metastasis			0·24			0·001
Present	20	22		20	23	
Absent	57	35		60	58	
Surgical margin			0·16			<0·001
Positive	27	18		29	22	
Negative	62	36		63	62	
HAI score			0·04			0·29
1–8	56	41		58	53	
9–18	41	15		42	44	

*Three postoperative deaths excluded. TNM, tumour node metastasis; HAI, hepatitis activity index. †Log rank test

Table 6 Independent prognostic factors for disease-free and overall survival by multivariate analysis

	Coefficient*	*P*	Risk ratio†
Disease-free survival			
HCV infection	1·03(0·43)	0·02	2·79 (1·21–6·50)
Portal vein invasion	0·91(0·42)	0·03	2·48 (1·10–5·60)
Overall survival			
Blood loss	2·09(0·65)	0·001	8·01 (2·29–28·69)
Surgical margin	1·71(0·51)	<0·001	5·54 (2·04–15·05)
Intrahepatic metastasis	1·13(0·54)	0·04	3·09 (1·07–8·90)
Portal vein invasion	1·10(0·50)	0·03	2·99 (1·11–8·03)
Extent of resection	0·96(0·45)	0·03	2·62 (1·09–6·28)

Values in parentheses are *standard errors or †95 per cent confidence intervals. HCV, hepatitis C virus

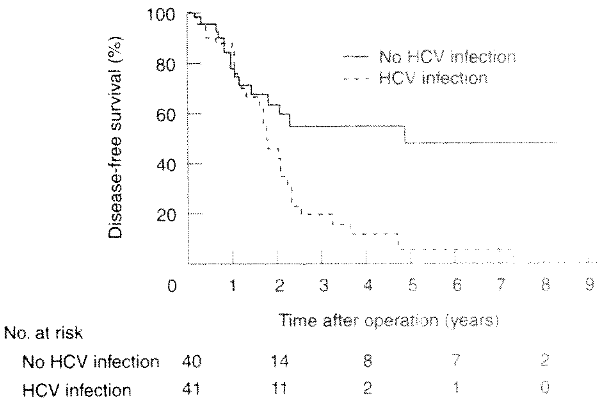


Fig. 2 Disease-free survival rates after hepatic resection in hepatitis C virus (HCV)-positive and HCV-negative patients. $P < 0{\cdot}001$ (log rank test)

Prognostic factors

In terms of tumour recurrence and overall survival, 14 clinical and biochemical and nine pathological factors were evaluated by univariate analysis (*Tables 4* and *5*). Factors that showed a significant difference by either the log rank or Wilcoxon test were further evaluated by multivariate analysis (*Table 6*). Blood loss, surgical margin, intrahepatic metastasis, portal vein invasion and extent of hepatic resection were independently associated with overall survival. However, only HCV infection and portal vein invasion were independent risk factors for intrahepatic tumour recurrence. Disease-free survival rates in HCV-positive and HCV-negative patients are shown in *Fig. 2* (5-year survival 6 *versus* 47 per cent; $P < 0{\cdot}001$, log rank test). Comparison between HBV-positive and HCV-positive patients is shown in *Fig. 3* (5-year survival 58 *versus* 6 per cent; $P < 0{\cdot}001$, log rank test). Five patients were duplicated in this analysis. *Fig. 4* shows the effect of portal vein invasion on disease-free survival (5-year survival 23 *versus* 34 per cent; $P = 0{\cdot}035$, log rank test). Patient sex, postoperative chemotherapy, presence of diabetes mellitus, ICG clearance, AFP level, operative time, presence of tumour capsule and liver fibrosis score were not significant predictors of disease-free survival or overall survival rates.

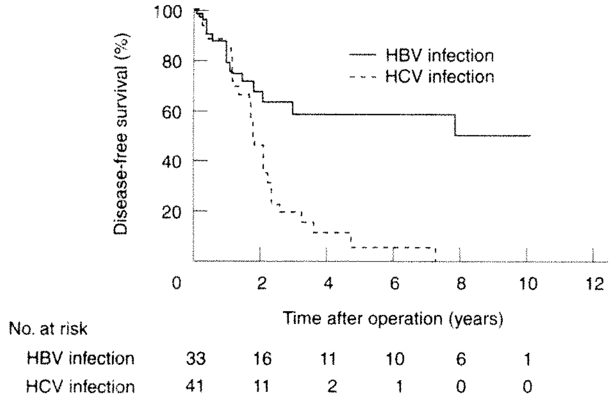


Fig. 3 Disease-free survival rates after hepatic resection in hepatitis B virus (HBV)-positive and hepatitis C virus (HCV)-positive patients. $P < 0{\cdot}001$ (log rank test)

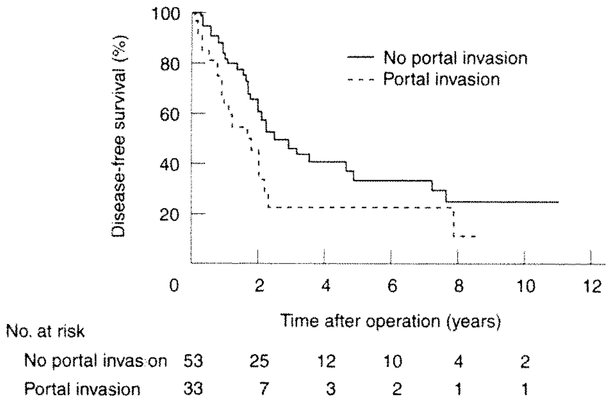


Fig. 4 Disease-free survival rates after hepatic resection in patients with and without portal vein invasion. $P = 0{\cdot}035$ (log rank test)

Discussion

The association between cirrhosis and HCC has been confirmed repeatedly and cirrhosis itself has been considered a precancerous lesion irrespective of its aetiology[21]. Nevertheless, HCC can develop in non-cirrhotic livers with an incidence of 10–40 per cent[22]. To date, there have been several important reports on clinicopathological differences between HCC with and without cirrhosis[22–24]. HCV infection has become the major aetiology of HCC in not only Japan[9] but also in Mediterranean countries[25]. Furthermore, the incidence of HCV-associated HCC is increasing year by year in Japan. It is likely that approximately 30 per cent of HCV-associated HCCs develop before cirrhosis is established[9]. HCC develops more often in non-cirrhotic livers with chronic hepatitis B. Recent detailed follow-up of patients with chronic hepatitis B and C has brought about earlier diagnosis of HCC in livers without cirrhosis[5–11]. However, over the past decade the surgical outcome of resection of patients with HCC but no cirrhosis has not improved despite improved perioperative management and extensive adjuvant therapy.

Despite numerous reports of the prognostic factors after resection of HCC, only a few studies have evaluated the risk factors for intrahepatic tumour recurrence and prognostic factors for survival in patients without cirrhosis[26–28]. Reviewing the reported series of HCC without cirrhosis (*Table 7*), the incidence of non-cirrhotic HCC ranged from 30 to 51 per cent, the resectability rate ranged from 44 to 87 per cent, and the operative morbidity and operative mortality rates were 19–43 and 3–7 per cent respectively.

Table 7 Results of hepatic resection for hepatocellular carcinoma without cirrhosis

Reference	Year	All cases of HCC	HCC without cirrhosis*	Hepatic resection*	Morbidity*	Death*	Overall survival rate (%)†			
							1 year	3 years	5 years	10 years
Smalley *et al.*[26]	1988	124	63 (51)	30 (48)	–	2 (7)	–	–	25	–
Bismuth *et al.*[27]	1995	222	79 (36)	68 (86)	13 (19)	2 (3)	74 (71)	52 (43)	40 (33)	26 (19)
Fong *et al.*[28]	1999	412	123 (30)	54 (44)	23 (43)	2 (4)	83	58	42	–
Present series		349	126 (36)	100 (79)	22 (22)	3 (3)	97 (79)	76 (38)	50 (31)	47 (22)

Values in parentheses are *percentages or †disease-free rates. HCC, hepatocellular carcinoma

The 5-year survival rate ranged from 25 to 50 per cent. Analysis of prognostic factors was performed by Bismuth *et al.*[27], who showed in a multivariate analysis that only age, sex and histopathological data predicted overall and disease-free survival. Tumour size and capsular invasion were prognostic factors for survival but only tumour size was a significant factor for tumour recurrence.

In the current study, univariate analysis revealed that many clinical and pathological factors were associated with overall and disease-free survival rates. In multivariate analysis, however, the independent prognostic factors for survival were portal vein invasion, intrahepatic metastasis (daughter nodules), surgical resection margin, extent of hepatic resection and blood loss. Significant independent risk factors for intrahepatic tumour recurrence were HCV infection and portal vein invasion. The discrepancy in prognostic factors for overall and disease-free survival may indicate that intrahepatic recurrence does not necessarily influence survival possibly because recurrence in patients without cirrhosis can be treated effectively by repeat hepatectomy, TAE or percutaneous ethanol injection.

Intrahepatic tumour recurrence can be attributed to progression of micrometastasis or metachronous carcinogenesis in the remnant liver. Although several methods are advocated for differentiating between the two, including X chromosome inactivation, detection of somatic mutations or HBV integration analysis, such studies were not performed in the current investigation. It may be assumed that intrahepatic recurrence from the first cause occurs earlier than that due to the second cause. Disease-free survival rates between HCC with and without portal vein invasion were significantly different during the first 2 years after operation (*Fig. 4*). As intrahepatic metastases are strongly associated with portal vein invasion, the rapid recurrence in the group with portal vein invasion could be attributed to the undetected micrometastases. On the other hand, the difference in disease-free survival between HCV-positive and HCV-negative patients was not observed during the first 1·5 years but became clear thereafter (*Fig. 2*), suggesting that the recurrence in HCV-positive patients is due to metachronous carcinogenesis.

In view of the high recurrence rate in HCV-positive patients, one may consider the place of liver transplantation for such patients. In fact, excellent 5-year survival rates have been reported for patients with HCC and HCV-associated cirrhosis[29,30]. The disease-free 5-year survival rate in this study was only 6 per cent but the overall 5-year survival rate was 39 per cent in HCV-positive patients. This can be explained by the fact that recurrent HCC in patients without cirrhosis can be treated more aggressively by re-resection, repeat TAE or ethanol injection than in cirrhotic patients. Nevertheless, liver transplantation may be indicated for selected patients with HCC and chronic hepatitis C, particularly for those with unfavourable tumour factors.

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Original article

Sympathetic autoregulation in peripheral vascular disease

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Background: Lower limb venous pressure increases on dependency, stimulating a local sympathetic axon reflex which triggers precapillary and arteriolar vasoconstriction. The resulting decrease in arterial calf inflow, known as the venoarteriolar response (VAR), is impaired in critical leg ischaemia. The aim of the study was to evaluate the VAR in symptomatic non-critical leg ischaemia and after restoration of leg perfusion following successful revascularization.

Methods: The study included 30 normal subjects, 30 patients with stable intermittent claudication and 30 patients with severe ischaemia who had undergone successful infrainguinal revascularization. In all patients the foot skin blood flow (flux) in the horizontal (HBF) and sitting (SBF) positions was measured using laser Doppler fluxmetry. The VAR was calculated as (HBF − SBF)/HBF × 100 per cent. The pressure that elicited the reflex (pVAR) was evaluated in the horizontal position.

Results: The median VAR was significantly lower in patients with stable claudication than in normal subjects or patients following successful revascularization (29·1 *versus* 59·5 and 63·9 per cent respectively; $P < 0{\cdot}0001$). Similar results were obtained for the pVAR (22 *versus* 45 and 40 mmHg respectively; $P < 0{\cdot}001$). There was no difference, however, in either the VAR or pVAR between normal individuals and patients following a successful bypass.

Conclusion: Patients with claudication had a significant impairment of orthostatic sympathetic autoregulation. After successful revascularization, and in spite of the extensive disease in the receiving circulation, this autoregulation returned to normal.

Presented previously to the Vascular Surgical Society in London, November 1997 and published in abstract form as *Br J Surg* 1998; **85**: 557

Paper accepted 21 November 2000

British Journal of Surgery 2001, **88**, 523–528

Introduction

The autonomic nervous system is an important regulator of leg blood flow, mediated through the sympathetic axon reflex acting on cutaneous, subcutaneous and muscular arterioles[1–4]. A postural change from lying to sitting or standing elicits a precapillary arteriolar vasoconstriction known as the venoarteriolar response (VAR), which is thought to play a protective role in capillary homoeostasis[5–12]. The VAR prevents a rise in capillary pressure that would result in increased capillary filtration, and the development of oedema[6,9,11–13].

Impairment of the VAR has been demonstrated in chronic venous insufficiency[6], diabetic autonomic neuropathy[7], nifedipine administration[8], the premenstrual syndrome[14], and with ageing[9]. In severe incapacitating claudication and critical or subcritical leg ischaemia due to peripheral vascular disease (PVD), isotope washout techniques have demonstrated a marked reduction or abolition of the orthostatic response[2,4,5,10,11,13,15]. However, contradictory data have been published regarding peripheral sympathetic function in patients with intermittent claudication. Henriksen and Paaske[1,2,4] and Morgan *et al.*[16] have reported minimal changes of the VAR in patients with claudication, whereas Belcaro *et al.*[11] and Cisek *et al.*[12] have indicated complete attenuation of the response in these patients. Using radioisotope washout techniques, Rordam *et al.*[5], Eickhoff[10] and Jelnes[15] have demonstrated that peripheral vasoregulatory mechanisms in patients with both rest pain and severe claudication can be restored to normal levels following arterial reconstruction.

Laser Doppler fluxmetry provides a non-invasive evaluation of skin blood flow in both arterial and venous disorders[6,11–13,17,18]. It gives a prompt evaluation of the VAR, without the potential risks of an invasive procedure or isotope exposure. In this study skin blood flow, its change with postural alteration and the venous pressure that is required to elicit this change were measured in normal individuals, patients with stable intermittent claudication and patients with severe incapacitating claudication or critical ischaemia who had had successful revascularization. The aim was to examine the status of peripheral sympathetic autoregulation and its sensitivity in advanced atherosclerosis, and after flow reconstruction for critical or subcritical ischaemia. If peripheral sympathetic autoregulation is impaired in symptomatic non-critical PVD, its reversal following successful revascularization should indicate that its function is a marker sensitive to arterial flow reduction, independent of the severity of the atherosclerosis. Reperfusion increases tissue flow, decreases tissue ischaemia, but does not alter the severity of atherosclerosis in the vascular bed beyond the distal anastomosis. Impairment of the VAR in legs of patients with claudication may represent a resetting of the variable component of peripheral resistance to flow, aiming at optimizing arterial compensation.

Materials and methods

This was a cohort study conducted in a tertiary referral university hospital, consisting of three groups: 30 normal control subjects, 30 patients with stable intermittent claudication due to infrainguinal PVD caused by superficial femoral artery occlusion, and 30 patients with infrainguinal PVD who had undergone successful femoropopliteal or femorodistal bypass grafting.

The inclusion and exclusion criteria are listed in *Table 1* and the demographics in *Table 2*. Normal subjects were recruited to match patients for age and sex. The prevalence of risk factors in the patients with PVD was not significantly different between surgical patients and patients with claudication. All subjects were asked to abstain from caffeine-containing drinks and smoking for over 12 h before the investigation. Risk factors in each group and ankle : brachial pressure indices (ABPIs) are recorded in *Table 2*, and details of the revascularization procedures in *Table 3*.

Table 1 Patient inclusion and exclusion criteria

Inclusion criteria
- No clinical symptoms or signs of PVD (control group)
- Resting and postexercise ABPI exceeding 0·9 (control and revascularization groups)
- Initial claudication distance 100–300 m on treadmill testing (claudication group)

Exclusion criteria
- Evidence of sensory neuropathy
- Use of vasoactive medications
- Chronic venous insufficiency
- Previous lumbar sympathectomy
- Inability to complete the exercise protocol
- Significant graft stenosis with diameter reduction exceeding 50% (after revascularization)

PVD, peripheral vascular disease; ABPI, ankle : brachial pressure index

The groups underwent the following examination protocol. (1) A full history was taken and physical examination carried out. (2) Venous colour flow duplex imaging was used to detect chronic venous insufficiency as described previously[19]. (3) Angiography or lower limb arterial duplex imaging was performed within 2 months in patients with claudication. (4) Duplex imaging was used to evaluate graft patency in the revascularization group (HP Sonos 2500® (Hewlett Packard, Palo Alto, CA, USA) 7·5/5·5-MHz probe). The presence of a stenosis was determined using real-time B-mode imaging, combined with gated Doppler ultrasonography. Peak systolic velocity was evaluated along the graft and the anastomoses, and patients with a ratio of stenotic to prestenotic velocity exceeding 2·0 were excluded[20]. (5) A standard lower limb arterial treadmill exercise test (speed 4 km/h, gradient 10 per cent) was

Table 2 Demographic details

	Control ($n=30$)	Claudication ($n=30$)	Revascularization ($n=30$)
Age (years)*	70 (66–75)	70 (60–75)	66 (55–72)
Sex ratio (M : F)	21 : 9	19 : 11	18 : 12
Risk factors			
Smoking†	8	21 (6)	19 (5)
Hypertension‡	6	15	12
Diabetes	1	6	9
High cholesterol‡	3	8	10
Ankle : brachial pressure index*			
Resting	1·06 (1·03–1·10)	0·60 (0·46–0·76)	0·97 (0·94–1·04)
After exercise	1·08 (1·02–1·12)	0·47 (0·32–0·65)	0·94 (0·91–1·02)

*Values are median (range); †values in parentheses are numbers of active smokers at the time of investigation; ‡includes patients on medication with normalized measurements at the time of study

Table 3 Clinical details in 30 patients who had femorodistal bypass

Age at surgery (years)*	64 (51–72)
Clinical status†	
Severe claudication	12 [0·65 (0·45–0·80)]
Rest pain	10 [0·32 (0·15–0·42)]
Gangrene/ulceration	8 [0·48 (0·35–0·55)]
Age of graft (months)*	20 (13–36)
Type of graft	
Above-knee femoropopliteal	7
Below-knee femoropopliteal	15
Femorocrural	8
Graft material	
Autogenous vein	26
Prosthetic	4

*Values are median (range); †Values in square parentheses are ankle brachial pressure indices, median (range)

performed and pre-exercise and postexercise (after 1 min) ABPIs were calculated. (6) Laser Doppler fluxmetry was performed to determine skin blood flux in the horizontal and sitting positions (Laserflo BPM403; Vasamedics, St Paul, MN, USA). The probe was secured on the dorsum of the foot using ring shaped double-sided adhesive tape. Measurements of skin blood flux were made after a 20-min rest and acclimatization in a temperature-controlled room (21–23°C). The recorder chart speed was set at 20 mm/min with an averaging time of 5 s and a sensitivity setting modified to allow maximal chart deflection to be recorded on the standard graph paper (× 20, × 100, × 400). The resting blood flux in the horizontal position (HBF) was averaged over 7 min; measurements were expressed in arbitrary flux units. The subjects were then placed in the upright sitting position with the feet in a stable dependent position. The sitting blood flux (SBF) was calculated over 7 min, with the initial 2 min discarded to allow for stabilization of the skin flux. The VAR was calculated as (HBF − SBF)/HBF × 100 per cent. (7) With the probe maintained at the same site, examined subjects resumed the horizontal position and skin blood flux returned to the HBF level. A blood pressure cuff was applied over the distal calf and inflated to 60–70 mmHg while flux was being monitored. At this level of applied pressure the HBF decreased and was maintained at a level equalling the SBF, simulating the changes documented with postural alteration. The cuff was then deflated at decrements of 5 mmHg until flux began to increase steeply towards the HBF level. The lowest level of applied pressure that maintained the SBF was defined as the pressure that elicits the VAR (pVAR). The spatial and temporal variability of the VAR, pVAR, HBF and SBF in five normal subjects and five patients with claudication is shown in *Table 4*.

Results are expressed as median (interquartile range). For statistical evaluation of the data, non-parametric analysis (Mann–Whitney *U* test) was performed with 95 per cent confidence intervals (c.i.) of the point estimate. The Bonferroni correction was applied. Statistical significance was assumed if $P < 0{\cdot}025$.

Results

There was no difference in the HBF between the study groups. However, when placed in the upright sitting position, skin flux was significantly higher among patients with claudication than in either the healthy individuals or those who had undergone revascularization ($P < 0{\cdot}001$)

Table 4 Variability of skin blood flux, venoarteriolar response and pressure that elicits it expressed as coefficient of variation in percentage range[21]

	Temporal (CV%)		Spatial (CV%)
	1 day 5 measurements	5 days 5 × 5 measurements	1 day 10 measurements
Normal subjects (*n* = 5)			
HBF	8–17	19–32	18–27
SBF	7–14	19–30	17–25
VAR	5–8	7–12	8–13
pVAR	5–7	7–10	7–12
Patients with claudication (*n* = 5)			
HBF	10–19	15–30	20–29
SBF	8–17	14–28	19–27
VAR	5–9	6–10	7–12
pVAR	6–8	7–11	6–10

CV, coefficient of variation; HBF, skin blood flux in the horizontal position; SBF, skin blood flux in the sitting position; VAR, venoarteriolar response; pVAR, venous pressure that elicits the VAR

(*Fig. 1*). In all groups and individual subjects skin blood flux was lower in the sitting than the horizontal position, so only positive VARs were recorded.

The percentage decrease in skin blood flux on sitting (VAR) was significantly higher in normal subjects ($P < 0·0001$; 95 per cent c.i. 22–36 per cent) and patients after revascularization ($P < 0·0001$; 95 per cent c.i. 28–41 per cent) than in patients with claudication. There was no significant difference between the first two groups ($P = 0·09$; 95 per cent c.i. –12 to 1 per cent) (*Fig. 2*).

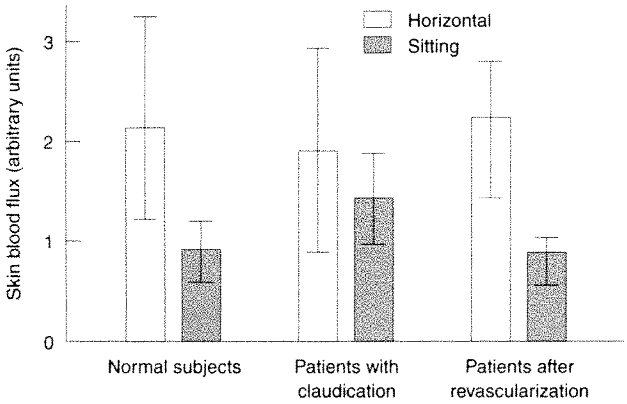

Fig. 1 Median (interquartile range) skin blood flux in horizontal and sitting positions in normal subjects, patients with stable intermittent claudication and patients after successful bypass grafting for severe peripheral vascular disease. There was no significant difference in flux in the horizontal position between the three groups. In the sitting position, skin flux in claudicants was higher than that in either normal or surgical patients ($P < 0·001$; Mann–Whitney *U* test)

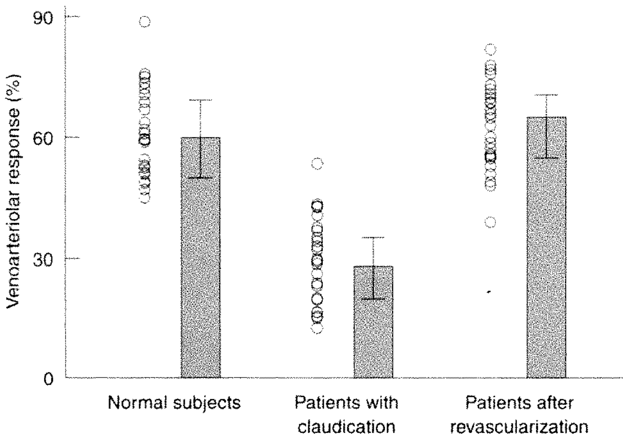

Fig. 2 The percentage decrease in skin blood flux on sitting (venoarteriolar response; VAR) in normal subjects, patients with stable intermittent claudication and patients after successful infrainguinal bypass grafting for severe peripheral vascular disease. Data are presented as combined scattergrams and error bars (median and interquartile range). The VAR was significantly lower in claudicants than in either normal controls or grafted subjects ($P < 0·0001$; Mann–Whitney *U* test). There was no significant difference between normal and surgical patients ($P = 0·09$)

The pressure that released the VAR (pVAR) was significantly lower in patients with claudication than in either normal subjects ($P < 0·001$; 95 per cent c.i. 18–28 mmHg) or patients after revascularization ($P < 0·001$; 95 per cent c.i. 9–19 mmHg). The pVAR was greater in normal subjects than after revascularization ($P = 0·04$), but the difference failed the corrected (Bonferroni) significance threshold (*Fig. 3*).

Discussion

The sympathetic autoregulatory response to alteration of posture is abolished in patients with critical leg ischaemia[2,4,5,10,11,13,15], but reported data on autonomic function in less severe PVD have been contradictory[1,2,4,11,12,16]. The present results demonstrate that the postural response is present but attenuated in patients with stable claudication, and that successful revascularization results in resumption of a normal autonomic response. Improvement in this response has been reported previously after successful vascular reconstruction, but the magnitude of improvement remains partially determined[5,10,12,15,22].

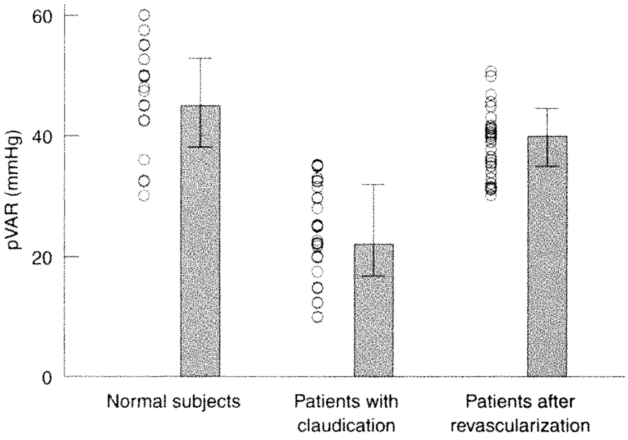

Fig. 3 Pressure that elicits the venoarteriolar response (pVAR) in normal subjects, patients with stable intermittent claudication and patients after successful bypass grafting for severe peripheral vascular disease. Data are presented as combined scattergrams and error bars (median and interquartile range). The pVAR was higher in either normal or grafted subjects than in claudicants ($P < 0·001$; Mann–Whitney *U* test). The pVAR in normal subjects was higher than that in patients who underwent surgery ($P = 0·04$), but the difference failed the corrected (Bonferroni) significance threshold

The postural autoregulatory response, i.e. the decrease in calf arterial inflow on dependency, is a physiological phenomenon of homoeostatic value to the tissues, exerting a protective role in maintaining a stable microcirculatory environment when pressure increases in the venous system. Described first by Gaskell and Burton[23] and later by Henriksen and Paaske[1,2,4], this response, termed the VAR, is brought about by a local sympathetic axon reflex on the arterioles in response to passive venous distension[1–13]. This results in an increase in peripheral resistance and a decrease in blood flow[1–13,16,23,24]. This vasoconstrictive response preserves systemic blood pressure in different postures, and prevents capillary pressure increase, interstitial fluid leakage and oedema formation[1,2,4,6,8,9,11–13,16,24].

Laser Doppler fluxmetry is an established method in the investigation of microcirculatory flow in health and disease[6,11–13,17,18]. It enables non-invasive measurement of cutaneous blood flow and its changes arising from alteration of posture. Red cell flux is proportional to the concentration and velocity of red cells flowing in the capillaries[13,17,18]. These variables are influenced significantly by the density of the capillaries, known to vary in the skin up to sixfold per mm^2, affecting the spatial and temporal variability of flux measurement[13,21,25]. By obtaining flux from the same position on the foot during a single examination setting and expressing the result as a ratio of flux values, the VAR can be estimated reproducibly[21] as differences in the temporal and spatial domains are nullified.

This study demonstrates that patients with stable intermittent claudication, with only a mild to moderate reduction in walking ability due to femoropopliteal PVD, have a significant increase in the arterial perfusion of cutaneous capillaries on dependency compared with normal subjects. This, in the absence of flux differences on recumbency, indicates that autoregulation is impaired at a relatively early stage in PVD, due either to sympathetic nerve damage or to physiological resetting of arterioles to optimize perfusion in the ischaemic leg.

Cutaneous capillary perfusion in patients who had had a successful infrainguinal reconstruction was the same as the level documented in healthy subjects, indicating that the autonomic regulation is not permanently impaired in PVD, even after a period of critical ischaemia. A recently performed study at this institution demonstrated that sympathetic function returns to normal following revascularization in less than 6 days[26]. This confirms previously published data by Rordam *et al.*[5] who reported return of the vasoconstrictor response by the third day after aortoiliac reconstruction for severe claudication. Assuming that nerve tissue repair requires several months, such early resumption of autonomic function after revascularization suggests that the mechanism is a physiological resetting rather than nerve regeneration.

The external pressure (pVAR) that triggers the sympathetic response to postural alteration (VAR), is another way of grading autonomic function. It was similar between normal subjects and patients following revascularization, confirming the resumption of sympathetic activity after restoration of arterial flow in severe PVD[27]. The significantly lower pVAR in patients with claudication suggests that, despite the presence of relative capillary vasodilatation, the sympathetic response triggers at a much lower threshold. This may reflect a compromise between limited perfusion reserves in the tissue on one hand and the presence of a functional and undamaged autonomic system on the other. The latter responds early to protect capillary homoeostasis from the transmitted pressure of unimpeded arterial inflow, secondary to arteriolar vasodilatation.

Resumption of autonomic sympathetic function after restoration of flow in patients with critical ischaemia indicates that the local sympathetic response is sensitive to flow derangement and thus local tissue ischaemia, rather than the degree of atherosclerosis present. Even after a successful infrainguinal bypass the degree of atherosclerosis in the distal circulation is unchanged. It could be suggested that patients who had revascularization with normalization of the resting ABPI and only minimal decline following exercise may not have had distal disease, explaining the optimization of autonomic function following surgery. However, atherosclerosis is a generalized disease, affecting virtually every vascular bed. In diabetics, peripheral neuropathy may be present in conjunction with autoregulatory dysfunction even with normal peripheral pulses[28]. In these patients, peripheral neuropathy is thought to be predominantly the product of anatomic and physiologic abnormalities in the microvasculature, associated with thickened capillary basement membranes and increased protein glycation, impairing the flux of nutrients and increasing the migration of leucocytes[29]. In this study, none of the diabetics with claudication, or after revascularization had clinical evidence of peripheral neuropathy; there was no difference in their sympathetic autoregulation compared with non-diabetic counterparts. Metabolic factors may hold a key role in autoregulation but results from this study clarify that sympathetic function resumes once flow is restored.

Although investigations were performed under resting conditions, it may be postulated that this impairment provides a compensatory mechanism to improve perfusion pressure both on resting and during exertion. Ischaemic rest pain is relieved by dependency of the leg, and abolition of the vasoconstrictor response allows an increase in perfusion pressure, thus reducing local ischaemia[2,4,5,10,11,13,15].

Following surgery, postreconstruction hyperaemia and lower limb oedema are marked[5,13,15,22], possibly secondary to prolonged vasoparalysis and delayed return in sympathetic arteriolar function, in combination with the lymphatic damage caused by the surgery[5,15,22].

In conclusion, patients with claudication have a significant impairment of the orthostatic response. After successful revascularization this response returns to normal. Reperfusion increases tissue flow and decreases ischaemia, but does not alter the severity of atherosclerosis in the distal vascular bed. Thus impairment of the orthostatic sympathetic response results from both localized flow reduction and chronic tissue ischaemia, and not the severity of underlying atherosclerosis. The VAR could be an alternative non-invasive means of quantifying the severity of PVD in patients with claudication.

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Original article

Variation in clinical decision making is a partial explanation for geographical variation in lower extremity amputation rates

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Background: Rates of lower extremity amputation vary significantly both between and within countries. The variation does not appear to support differences in need as an explanation. This study set out to see if variations in clinical decision making might contribute to the explanation.

Methods: Based on an extensive audit database of lower extremity amputations and revascularization operations, a decision model was produced. Drawing on items in this model allowed the selection of six clinical cases that differed in their probability of having amputation as the outcome. Two cases had 80 per cent or more, two cases had 45–55 per cent and two cases had 20 per cent or less probability of amputation. Each of ten consultant vascular surgeons looked at these cases without knowledge of their probability of outcome and decided on amputation or revascularization.

Results: Overall the chance-adjusted level of agreement (kappa coefficient) between the decisions made by ten surgeons on the six clinical cases and the actual outcome was 0·46, indicating a moderate level of agreement. The kappa coefficient for individual surgeons showed complete agreement ($\kappa = 1$) for four, substantial agreement ($\kappa = 0{\cdot}66$) for four, fair agreement ($\kappa = 0{\cdot}32$) for one and no agreement other than at a chance level ($\kappa = 0$) for one surgeon.

Conclusion: Variations in the clinical decisions made by vascular surgeons given the same patient are likely to explain at least a part of the observed geographical variation in rates of lower extremity amputation. Consensus guidelines may enable more consistent decision making for this problem.

Paper accepted 3 December 2000

British Journal of Surgery 2001, 88, 529–535

Introduction

There is now a large volume of research-based evidence that geographical variations in medical and surgical therapies and procedures arise for reasons that are not primarily explicable in terms of the practice of evidence-based medicine[1–6]. The factors that determine whether a particular decision is likely in clinical practice have been studied and seem to be classifiable in terms of factors specific to individual patients, to individual clinicians and to the context of the decision itself[7–9]. Among the first category are included the symptoms and signs that patients complain of or are found on examination[7]. Clinicians themselves tend to engage in different forms of decision-making processes dependent on the level of past experience and, thus, current level of expertise[10]. Contextual factors relate to the social, economic and organizational environment that the clinician and patient meet in and which thereby characterizes the consultation[11].

Advocates of more open clinical decision making cite studies which show that it is both possible and desirable to share the clinical decision-making process with the patient[12]. Such a change in clinical practice is claimed as ethical[13], clinically useful[14] and desirable from a medico-legal viewpoint[15]. Moreover, if there was a shared evidence base, shared decision making would be useful in institutionalizing evidence-based practice which might, in its effects, tend to eliminate all geographical and other varieties of variation in treatment not based on good reasons[16].

In a recent study of the rate of lower extremity amputations it was shown that between different centres in different countries there was significant variation[17]. Three centres in Northern England, here designated A, B and C, showed differences in all (first or repeat) amputation rates with age-standardized rates of 19·9, 27·8 and 20·2 per 100 000 for men, and 10·2, 8·4 and 8·8 per 100 000 for women respectively[17]. Indeed, over 1 year, 1997–1998, the all-person (95 per cent confidence interval (c.i.)) age-standardized rates for people with diabetes mellitus were 403 (300–506), 548 (355–740) and 865 (625–1105) respectively[18]. The authors of the Global Extremity Amputation Study (GLEAS) commented that in all centres diabetes mellitus was a major disease risk factor; variation in the prevalence of peripheral vascular disease was also a possible underlying reason for observed variations, especially where populations differed in demographic risk factors such as the prevalence of certain ethnic minorities[17].

This study is a follow-up investigation in the three centres in Northern England (A, B and C) which took part in the earlier study. The purpose of the current study was to explore possible reasons for the observed variation in lower extremity amputation rates between the three centres focusing, in particular, on the relevant processes of clinical decision making in each centre.

Materials and methods

The possible reasons for observing significantly different rates of lower extremity amputation are shown in a flow chart (*Fig. 1*). The methods used in this study were chosen to examine several possibilities (prevalence of diabetes mellitus; accessibility, use and quality of diagnostic and secondary prevention facilities; accessibility of vascular surgical expertise; and clinical decision making), with a focus on the latter explanation.

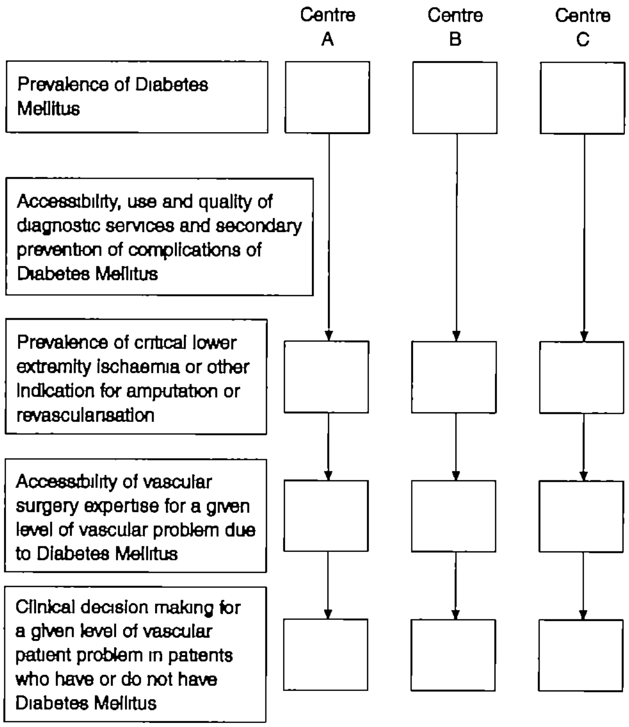
Centre A
Centre B
Centre C
Prevalence of Diabetes Mellitus
Accessibility, use and quality of diagnostic services and secondary prevention of complications of Diabetes Mellitus
Prevalence of critical lower extremity ischaemia or other indication for amputation or revascularisation
Accessibility of vascular surgery expertise for a given level of vascular problem due to Diabetes Mellitus
Clinical decision making for a given level of vascular patient problem in patients who have or do not have Diabetes Mellitus

Fig. 1 Flow chart showing possible stages in the development of clinical indications for lower extremity amputation and the levels at which research should seek a possible explanation for the observed geographical variation in rates

Prevalence of diabetes mellitus

Diabetes mellitus accounts for approximately 40 per cent of all underlying causes of critical lower extremity ischaemia, one major clinical reason for amputation[17]. Moreover, it is unlikely that other indications such as peripheral vascular disease or trauma vary sufficiently within one relatively small geographical area to explain observed variations[17]. Consequently, differing prevalences of diabetes mellitus in each of the centres A, B and C is a possible reason for differing amputation rates. The GLEAS study considered the demographic associations in each centre A, B and C for diabetes mellitus and concluded that the observed variation in rates could not be explained by differences in prevalence of diabetes mellitus[17].

Accessibility, use and quality of diagnostic and secondary prevention facilities

Given that variation in other indications for amputation, particularly peripheral vascular disease, is unlikely in these three centres, because of the close similarities in the relevant demographic risk factors, particularly prevalence of ethnic minorities[19], it is again necessary to focus on diabetes mellitus. An audit of available services was carried out by one of the authors (S.C.) who conducted face-to-face interviews with key professional staff in each of the centres. The audit involved extensive interviews with at least five professionals in each of the three centres. Questions were asked in a semistructured interview, interviews were taped and a thematic analysis for relevant contents was carried out (S.C.) and checked by another researcher (M.A.). *Table 1* summarizes information gathered for this audit.

Accessibility of vascular surgery expertise

In each centre 15 sets of notes on patients with diabetes mellitus were selected randomly from outpatient clinics conducted during the previous 3 years. In each case one author (S.C.) produced a summary of the history and presenting complaints as available in the patient's clinical notes. Past history, including any microvascular or macrovascular complications of diabetes mellitus, time since onset of the disease and the type of treatment received, was also gathered systematically and entered on to a predesigned protocol form. All references to the decision made by the vascular clinician and the source centre were excluded. The protocol forms from the three centres were then given a random code and were presented randomly to another researcher (J.C.) who graded each patient as showing mild, moderate or severe complications of diabetes mellitus (*Table 2*).

Clinical decision making

In one of the centres (A) the vascular surgeons had kept records for the purpose of clinical audit on all patients who had undergone either a lower extremity amputation or revascularization in the centre during the past 5 years. Each item of information was collected because the surgeons considered it important in patient management. In addition to the audit database, operation lists and clinical notes were consulted to add any missing cases of revascularization that were conducted during the period covered by the database. The database was also validated through checks from a separate comprehensive register of lower extremity amputations that was assembled for the GLEAS study[17]. This complete database was then used to model the dichotomous outcome amputate/do not amputate. *Table 3* shows the odds ratios for each of the factors found to be significant in a logistic regression model of this outcome.

Table 1 Information gathered for the audit of accessibility and facilities in each centre

General population size and area
Sex ratio
Diabetic centres
Number of patients registered in diabetic centre
Number of diabetologists
Patients seen per week
Facilities on site
Number of podiatrists
Foot clinics held
Number of patients seen in foot clinic
Food education given
Previous vascular surgery situation
Number of vascular surgeons
Vascular clinics held
Theatre time
Referral times to vascular team
Facilities available
Vascular practices/policies
Diabetic patients seen by vascular surgeon
Other factors (diabetes)
Other factors (vascular surgery)
Other factors (podiatry services)

Table 2 Ranking of severity of diabetes mellitus complications amongst referrals to vascular surgeons in three centres

	Severity of diabetes mellitus		
Centre	Mild	Moderate	Severe
A*	6	5	3
B*	5	4	5
C	5	8	2

$\chi^2 = 3{\cdot}05$, 4 d.f., $P > 0{\cdot}10$. *One set of notes unclassifiable

Using the logistic regression model it was possible to obtain a probability function that would yield the individual probability of amputation for each patient on the database (*Appendix*). Three pairs of patients were then chosen at random with a probability of amputation of 80 per cent or more, between 45 and 55 per cent, and 20 per cent or less. Each case chosen was then used as a clinical scenario which was produced to comprise a presenting complaint, history of presenting complaint, past medical history and findings from a clinical examination by a vascular surgeon (including, where available, results of any bedside investigation requested by the clinician). In particular the scenarios presented a spectrum of clinical indicators from claudication to critical ischaemia. An extensive amount of additional information was available for each patient (*Table 4*); this information was not presented routinely but each item was available if the clinician specifically requested it. The six clinical scenarios were sequenced randomly before being presented to each of ten vascular surgeons, all of whom had been employed in one or other of the three centres during the period relevant to the scenarios and were therefore eligible for this study. None of the eligible surgeons refused the request for interview. In each centre the surgeon was interviewed and asked to (1) make a decision regarding amputation of the lower extremity and (2) indicate on a ten-point scale how certain they felt about their decision (0, not at all certain; 10, completely certain). Each interview was tape recorded and the sequence of any additional requests by the surgeon for information on each scenario was noted. The data on 'certainty' and the qualitative information on additional information requests will be analysed in a further study. Each interview was conducted by one author (M.A.) with another (S.C.) acting as a source of any further information from items assembled for each case. This allowed smooth conduct of the session, which took between 25 and 40 min.

Statistical analysis

Contingency tables were analysed by χ^2 methods[20]. Agreement between an individual surgeon's decision and the actual outcome for each case scenario was calculated using the kappa statistic[20]. Values of kappa of 0–0·20 represent poor agreement, 0·21–0·40 fair agreement, 0·41–0·60 moderate agreement, 0·61–0·80 substantial agreement and 0·81–1·00 almost perfect agreement compared with chance[20]. The association between the probability level of the scenarios and each surgeon's

Table 3 Logistic regression model of decision making in cases of possible lower extremity amputation or revascularization

Predictor	Coefficient	Standard deviation	Z	P	Odds ratio
Constant	−1·59	0·61	−2·58	0·010	
Sex (M = 0)	−0·66	0·37	−1·80	0·071	0·51 (0·25–1·06)
Age					
(22–63 years = 0)					
63·1–71·8 years	−1·15	0·48	−2·37	0·018	0·32 (0·12–0·82)
71·9–79·0 years	−1·21	0·51	−2·38	0·017	0·30 (0·11–0·81)
79·1–95·0 years	−0·05	0·48	−1·10	0·922	0·95 (0·37–2·45)
Indication					
(Claudication or other = 0)					
Critical ischaemia	1·92	0·59	3·23	0·001	6·82 (2·13–21·85)
Diabetes					
(None = 0)					
IDDM	1·36	0·37	3·66	0·000	3·91 (1·88–8·11)
Hypertension					
(None = 0)					
Treated with single drug	−0·34	0·40	−0·84	0·398	0·71 (0·32–1·57)
Treated with more than one drug	−1·87	0·81	−2·31	0·021	0·15 (0·03–0·76)
Hyperlipidaemia					
(None = 0)					
Mild increase or type II–IV or strict diet or diet and drugs	−0·88	0·60	−1·48	0·138	0·41 (0·13–1·33)
Renal disease					
(None = 0)					
Creatine level 132–264 mmol/l or 265–530 mmol/l or > 530 mmol/l, or dialysis or transplant	1·76	0·57	3·07	0·002	5·82 (1·89–17·94)

Values in parentheses are 95 per cent confidence intervals. Two hundred and ten cases used; 11 cases contained missing values. Concordant pairs 81·8 per cent, discordant pairs 16·6 per cent, ties 1·6 per cent. IDDM, insulin-dependent diabetes mellitus

Table 4 Information available for each clinical scenario

Presented in all interviews	Available if requested
Presenting complaint	Full blood count
History of presenting complaint	Urea and electrolytes
Past medical history	Blood glucose (fasting)
Current medication	Ankle : brachial blood pressure index
Results of a clinical examination by a vascular surgeon	Angiography
Results of any bedside investigation performed by vascular surgeon	Plain chest and abdominal radiography Electrocardiography
Photographs of foot (presented in three scenarios)	Doppler ultrasonography scans Social worker report Occupational therapist report

expressed degree of 'certainty' regarding amputation or revascularization was calculated using Pearson's product–moment correlation[21]. The degree of 'certainty' for revascularization was transformed into the degree of 'certainty' regarding amputation by subtracting the stated value from 10 and multiplying by 10. 'Certainty' is calculated as stated value multiplied by 10.

Results

Results are presented separately for each possible explanation for the variation in rates (*Fig. 1*).

Prevalence of diabetes mellitus

The GLEAS study ruled out differing prevalence as a likely explanation for the differing amputation rates; the one exception was the Navajo area of the Indian Health Service, USA[17]. In particular, for the three centres A, B and C census data show that age structures, social class structures and ethnic minority structures are very similar[19]. These results tend to exclude any significant differences in the prevalence of diabetes mellitus.

Accessibility, use and quality of diagnostic and secondary prevention facilities

Table 1 shows the information gathered for the audit. When the data were analysed there were no major differences in the available facilities or in the perceived accessibility of these services. While this audit on its own cannot be said to

Table 5 Agreement between actual outcomes and individual surgeon's decisions: crude agreements and agreements adjusted for chance

	Surgeon									
	1	2	3	4	5	6	7	8	9	10
Overall agreement with actual outcome (%)	100	100	83	83	50	83	66	83	100	100
Chance-adjusted agreement with actual outcome (κ)	1·0	1·0	0·66	0·66	0·0	0·66	0·32	0·66	1·0	1·0
κ for each scenario probability										
Level of amputation										
Low	1·0	1·0	1·0	1·0	0·0	1·0	0·0	1·0	1·0	1·0
Middle	1·0	1·0	0·0	0·0	1·0	1·0	0·0	0·0	1·0	1·0
High	1·0	1·0	1·0	1·0	0·0	0·0	1·0	1·0	1·0	1·0

κ = 0·0–0·20, poor agreement; κ = 0·21–0·40, fair agreement; κ = 0·41–0·60, moderate agreement; κ = 0·61–0·80, substantial agreement; κ = 0·81–1·00, almost perfect agreement. Overall κ = 0·46 for all case scenarios and all surgeons

be decisive it should be taken together with the results of the investigation regarding the accessibility of vascular surgical advice given a similar level of problem (see below).

Accessibility of vascular surgical expertise

On the basis of a blind classification of three randomly selected sets of outpatient cases there was no evidence for any difference in the proportions of patients who consult a clinician with what may be classified as severe, moderate or mild vascular complications of diabetes mellitus (*Table 2*). The proportions of each level of vascular complications of diabetes mellitus may be expected to vary as a result of the availability, accessibility, use and quality of diagnostic and secondary prevention facilities. This finding also strengthens the conclusion that accessibility to vascular surgical advice was not an adequate explanation in this study.

Clinical decision making

The logistic regression model showed that age, sex, clinical indications, diabetes mellitus, hypertension, hyperlipidaemia and renal disease were all independent predictors of the decision whether or not to amputate the lower limb (*Table 3*). After the clinical indication critical ischaemia (*versus* claudication, infection or deformity) and presence of renal impairment, the presence of diabetes mellitus was the strongest predictor of an amputation outcome. The odds ratio (95 per cent c.i.) was 3·91 (1·88–8·11), indicating that diabetes mellitus increased the risk of amputation nearly fourfold in this population of patients. Increasing age and female sex decreased the risk of amputation while presence of renal impairment strongly increased the risk (OR 5·82 (1·89–17·94)).

Based on clinical cases with different levels of these predictors the overall and chance-adjusted agreement (kappa) between the decision made by each of ten surgeons and the actual outcome is shown in *Table 5*. Also shown is the kappa statistic for each surgeon stratified by the probability level of amputation derived from the model. Four surgeons showed perfect agreement ($\kappa = 1$), four surgeons showed a substantial level of agreement ($\kappa = 0{\cdot}61$–$0{\cdot}80$), one surgeon showed a fair level of agreement ($\kappa = 0{\cdot}21$–$0{\cdot}40$) and one surgeon had a poor level of agreement ($\kappa = 0$–$0{\cdot}20$). When the decisions made by all ten surgeons were compared with the actual outcome the kappa statistic was 0·46, a moderate level of agreement[20].

Table 6 shows the degree of 'certainty' regarding a decision to amputate classified by the probability of amputation of the scenario. The Pearson correlation coefficient was 0·653 ($P < 0{\cdot}001$).

Discussion

Presenting clinical cases derived from a comprehensive patient database kept in one centre to surgeons working either in that centre or in one of two other centres showed that the overall chance-adjusted agreement (kappa) between the vascular surgeons' decisions and the actual decision to amputate or revascularize a lower limb was $\kappa = 0{\cdot}46$. This indicates only a moderate level of agreement. Individual surgeons varied in their kappa levels, from perfect agreement to no agreement. This difference was not due to differences in the volume of work dealt with in each centre. In the discussion of possible reasons for the observed variations reported in the GLEAS project[17] the authors state: '[Excluding one population, the Navajo] differences

Table 6 Percentage level of certainty concerning the clinical decision of each of the ten surgeons

	Case					
	A	B	C	D	E	F
Amputation probability predicted by model (%)	22·8	84·5	47·1	55·2	84·6	18·6
Level of certainty of surgeon (%)						
Surgeon 1	R: 70 (30)	A: 90	R: 50 (50)	A: 90	A: 100	R: 80 (20)
Surgeon 2	R: 80 (20)	A: 100	R: 40 (60)	A: 100	A: 100	R: 90 (10)
Surgeon 3	R: 70 (30)	A: 100	A: 80	A: 70	A: 100	R: 100 (0)
Surgeon 4	R: 80 (20)	A: 90	A: 60	A: 90	A: 100	R: 100 (0)
Surgeon 5	A: 100	R: 30 (70)	A: 100	A: 100	A: 100	R: 100 (0)
Surgeon 6	R: 50 (50)	R: 30 (70)	R: 90 (10)	A: 90	A: 90	R: 100 (0)
Surgeon 7	A: 50	A: 80	A: 90	A: 50	A: 100	R: 90 (10)
Surgeon 8	R: 40 (80)	A: 60	A: 90	A: 60	A: 60	R: 80 (20)
Surgeon 9	R: 80 (20)	A: 80	R: 50 (50)	A: 100	A: 80	R: 90 (10)
Surgeon 10	R: 80 (20)	A: 70	R: 80 (20)	A: 100	A: 90	R: 90 (10)

Values in parentheses are transformed revascularization values (100 – stated value). A, amputation; R, revascularization

between the other populations did not seem to be related to the prevalence of diabetes; it seems likely that differences in the prevalence of peripheral vascular disease are important. Other factors, such as cultural and medical care differences, including access to vascular surgery services, may also be important but require further investigation'.

The three centres showed only a very small amount of geographical variation in peripheral vascular disease and trauma-associated amputations[17]. Another possibility cited in the GLEAS project was variation in availability or accessibility of vascular surgery facilities. These possibilities were considered in the current study but did not appear to offer an adequate explanation. A curious omission from the above listing of possible reasons for observed variations in rates is the possibility of differences in clinical decision making, although it is possible that the GLEAS authors' reference to variations in 'culture' may have been meant to cover this issue. The current study shows that this source of variation is likely to explain substantially the observed variation in rates, at least in the three centres studied here.

Using regression techniques to model decision making (so called 'policy capturing') originated 40 years ago[22]. It has been shown to be a very robust technique[23] producing outcomes which accord with the clinician's own choice regarding best practice[24]. In the current study such a policy capturing model was used as the 'standard' from which the six real clinical scenarios were derived. Employing clinical scenarios to explore variations in clinical decision making has been shown to be a useful method in a variety of decision situations[25–27]. The 'reality' of the scenario format (for instance simulated patients or written scenarios) does not seem to influence the responses elicited[28] and the scenarios used in the current study were actual cases, improving their face validity[29]. Although presenting clinical scenarios is, of course, artificial there was a significant correlation between the inherent uncertainty of the scenario (measured by the case probability of amputation) and the degree of 'certainty' about amputation assigned by the surgeons. This is taken to indicate that the scenarios were accurate reflections of the actual case uncertainty. Furthermore, although an actual decision may be made over an extended period of time, the case scenarios used allowed somewhat for this by including information on clinical course and the results of investigations.

In conclusion, this study shows that clinical decision making is not a precise and fully reliable activity. Given the same complex clinical situation, individual clinicians use their judgement and experience to make decisions and these decisions vary. However, even though experienced clinicians can and do differ in their decision making, it is far too early to attempt to say what constitutes a 'good' or a 'bad' decision. Rather it seems that there is scope for further investigation of clinical decision making in this area to explore, in particular, whether there is any consensus on what is a 'good' or 'bad' decision and whether it is possible to produce acceptable, valid and reliable guidance for surgeons faced with the decision of whether to amputate or revascularize a lower limb.

Acknowledgements

The authors thank the vascular surgeons and other professionals who agreed to be interviewed. Dr David Bowers gave statistical advice and Dr Richard Unwin commented on the methods and findings. This research was supported by funding from the M6 Suspense Fund and was produced as part of the NHS Executive Northern and Yorkshire Research and Development Portfolio Programme at the Nuffield Institute for Health.

Appendix

Given a logistic model

$$w = a + b_1 x_1 + b_2 x_2 \ldots b_n x_n$$

where $w = \log_e(P/1 - P)$ and P is the probability of a defined event y, a is a constant, $x_1 \ldots x_n$ are prognosis variables, and $b_1 \ldots b_n$ are coefficients, then rearranging

$$P(y) = [1 + e^{-(a + b_1 x_1 + b_2 x_2 \ldots b_n x_n)}]^{-1}$$

which gives the probability of the event y for a particular case characterized by the values of $x_1 \ldots x_n$.

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Original article

Fate of hypertension after repair of coarctation of the aorta in adults

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Background: Unrepaired aortic coarctation is known to have a detrimental effect on survival. The benefit of coarctation repair on systolic hypertension in adults has been questioned. This retrospective study was conducted to evaluate the impact of repair of aortic coarctation on systolic hypertension in adults.
Methods: Repair of aortic coarctation was performed in 84 patients aged 16–54 (mean 29) years. All patients were hypertensive before surgical intervention (mean systolic blood pressure 162 mmHg; mean diastolic blood pressure 93 mmHg). All patients underwent echocardiography and/or cardiac catheterization. The peak mean systolic gradient across the coarctation was 60 mmHg. The patients were followed after coarctation repair for between 1 and 12 (mean 5·2) years.
Results: There was significant regression of hypertension ($P < 0{\cdot}001$) in all patients. Thirty-five patients (42 per cent) did not need any antihypertensive medication 3 months after surgery. The prevalence of hypertension at the last follow-up (after mean 5·2 years) was 31 per cent.
Conclusion: Surgical repair of coarctation of the aorta in adults leads to regression of systolic hypertension and a decreased requirement for antihypertensive medication.

Paper accepted 3 December 2000

British Journal of Surgery 2001, 88, 536–538

Introduction

Coarctation of the aorta represents 5–8 per cent of patients treated for congenital heart disease[1]. Owing to rapid advances in early diagnosis and management, coarctation of the aorta is now rarely encountered in adults. Unrepaired aortic coarctation results in high morbidity and mortality from hypertension, myocardial infarction, heart failure, intracranial haemorrhage, aortic rupture, infective endocarditis and coronary artery disease[2,3]. Ninety per cent of untreated patients die from one of these complications before the age of 50 years[4]. The first surgical repair of this congenital anomaly was reported by Crafoord and Nylin in 1945[5]. Several studies have revealed that the success of elective repair diminishes with increasing age at operation[2,6]. The repair of coarctation of the aorta in adults has been reported to be associated with poor resolution of hypertension[2–4]. This study was undertaken to evaluate the fate of hypertension after surgical intervention in adult patients with coarctation of the aorta, in a South Indian population.

Patients and methods

Between January 1981 and December 1997, 84 adult patients underwent repair of coarctation of the aorta. There were 59 men and 25 women with a mean age of 29 (range 16–54) years. There were only two patients over 50 years of age (*Fig. 1*). Preoperative blood pressure measurements were obtained by simultaneous cuff pressure measurements in the right arm and legs. Hypertension was defined as systolic blood pressure in the right arm exceeding 140 mmHg[7]. The gradient across the coarct segment was measured by echocardiography and/or catheterization. The patients were divided into groups depending on the number of antihypertensive agents taken before surgery. These drugs included diuretics, angiotensin-converting enzyme (ACE) inhibitors, β-blockers and calcium channel blockers. The number of antihypertensive drugs each patient was taking before surgery was compared with the drug intake after surgical intervention at last follow-up (*Table 1*).

All patients were operated through a left posterolateral thoracotomy. In 80 patients the aorta was repaired using an aortic occlusion clamp with controlled hypotension. Atriofemoral bypass was used in two patients and in two patients a proximal-to-distal aortic shunt was used. Continuous perioperative cerebrospinal fluid drainage was employed in 16 patients. Forty-two patients (50 per cent) underwent excision of the coarct segment with end-to-end anastomosis, 18 (21 per cent) underwent patch aortoplasty, 12 patients (14 per cent) had resection of the coarct segment with graft interposition and 12 (14 per cent) had a jump bypass graft. Re-exploration was needed in four patients for control of postoperative bleeding.

Follow-up ranged from 1 to 12 (mean 5·2) years. Follow-up included assessment of blood pressure in all four limbs at the time of discharge from hospital, then monthly during the first year and every 3 months thereafter. All patients had echocardiography 3 months after surgery for assessment of the surgical outcome and estimation of any residual gradient.

Results

All patients had systolic hypertension at the time of admission. The mean systolic blood pressure was 162 (range 140–210) mmHg and the mean diastolic blood pressure was 93 (range 60–110) mmHg. The mean systolic gradient across the coarct segment assessed by Doppler echocardiography was 60 (range 25–154) mmHg. The gradient across the coarct segment could not be assessed in six patients who had very little forward flow in the aorta. The aorta was filling from collaterals in the latter patients on aortography. One patient died from uncontrolled haemorrhage after operation. Two patients had transient paraparesis, both of whom recovered within 2 weeks. Sixty-three patients had paradoxical hypertension after surgery which disappeared within 24–48 h. The mean(s.d.) postoperative gradient across the repaired segment was 11(4) mmHg. Of the 83 surviving patients, 48 were hypertensive 3 months after surgical intervention; only 26 patients were hypertensive at the last follow-up (*Table 1*). However, in these patients hypertension was controlled with one or more antihypertensive agents.

Poor resolution of hypertension was mostly seen in patients over the age of 30 years at the time of repair (*Fig. 1*). Two patients had a significant residual gradient (35 and 28 mmHg) after repair of coarctation of the aorta. Both were managed successfully with balloon dilatation 6 months after surgery.

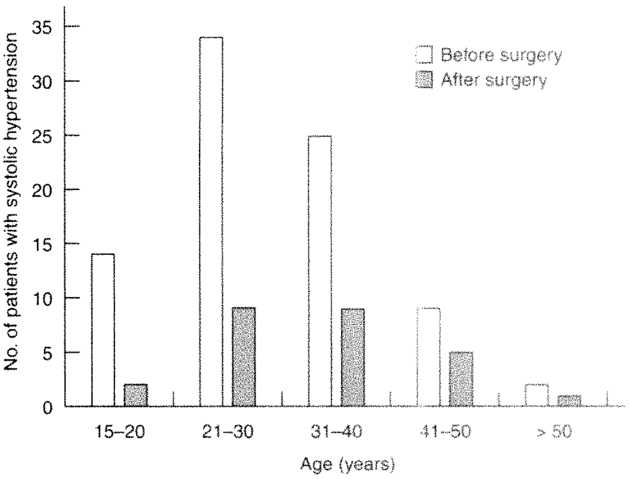

Fig. 1 Age distribution and status of hypertension before and after repair of coarctation of the aorta

Table 1 Distribution of patients with systolic hypertension before and after surgery

Antihypertensive medication	Before surgery (n=84)	After surgery: 3 months (n=83)	After surgery: Last follow-up* (n=83)
None	3	35	57
One drug	32	26	15
Two drugs	30	13	8
More than two drugs	19	9	3

*Mean 5·2 years

Discussion

Most patients with uncorrected coarctation of the aorta die before the age of 50 years[3]. Hypertension is an established major risk factor for cardiovascular disease leading to premature death[2,7]. Age at the time of initial repair of coarctation of the aorta is the most important predictor of late hypertension[1,3,7]. Despite a satisfactory reduction in blood pressure soon after operation, studies with longer follow-up have demonstrated that about one-third of patients develop late hypertension[8,9]. Clarkson *et al.*[10] showed that the prevalence of late hypertension increased with the duration of follow-up. Several factors have been implicated in the persistence of hypertension after the repair of coarctation. These include endocrine factors and poor compliance of the arterial tree proximal to the coarctation site[11]. Abnormal endothelium-mediated vasodilatation in normotensive adults following coarctation repair suggests that abnormal endothelial function may contribute to the pathogenesis of hypertension[12]. Koller *et al.*[13] observed the lowest incidence of late hypertension (10 per cent) in children who had surgery between the ages of 2 and 9 years. Lawrie *et al.*[14] observed severe late hypertension in only 11 per cent of patients when the coarctation was repaired before the age of 13 years. Maron *et al.*[2] noted that 37 per cent of patients were hypertensive 11–25 years after coarctation repair. Kappetein *et al.*[15] reported that 49 per cent of their patients were hypertensive, but the patients were under 3 years of age at the time of surgery and there was a high prevalence of recoarctation.

Olley[6] suggested that operation may not be indicated for patients over 25 years of age, owing to lack of evidence that it alters the natural history of coarctation. However, Wells and colleagues[16] reported 26 adult patients with a follow-up of 1–7 years after coarctation repair who had a significant improvement in systolic hypertension. In the present study, 35 patients (42 per cent) did not need any antihypertensive medication after operation but the rest needed one or more antihypertensive drugs to achieve a systolic blood pressure of less than 140 mmHg (*Table 1*). However, the hypertension was controlled with drugs, even in patients who had failed medical treatment before surgical intervention. The mean systolic blood pressure after coarctation repair was 127 (range 100–180) mmHg; all patients had a significant improvement in systolic hypertension ($P < 0{\cdot}001$) compared with preoperative values (*Fig. 1*). The prevalence of late postoperative hypertension in this series was 31 per cent.

Aris *et al.*[17] reported repair of aortic coarctation in eight patients over 50 years of age. The systolic hypertension regressed in all patients and the need for antihypertensive medication was reduced. In the present study, only two patients were aged over 50 years; one became normotensive after surgery and the other required an ACE inhibitor to control the hypertension.

Bearing in mind the low risk of surgery in this series, repair of coarctation of aorta can be recommended in adults. The surgery leads to regression of systolic hypertension and the need for antihypertensive medication is reduced.

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Original article

Immune-stimulating effects of low-dose perioperative recombinant granulocyte–macrophage colony-stimulating factor in patients operated on for primary colorectal carcinoma

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Background: Surgery induces a postoperative immunosuppression, thereby possibly facilitating the outgrowth of pre-existing occult metastases or the seeding of disseminated tumour cells in patients with primary colorectal carcinoma operated on with curative intent. The hypothesis that adjuvant therapy with perioperative recombinant human granulocyte–macrophage colony-stimulating factor (rhGM-CSF) would minimize postoperative immunosuppression was investigated in this pilot study.

Methods: Patients were allocated randomly to receive daily subcutaneous injections with either saline ($n = 8$) or rhGM-CSF 2·8 μg per kg body-weight ($n = 8$) from 3 days before operation until 4 days afterwards. Phytohaemagglutinin (PHA) skin test reactivity, monocyte human leucocyte antigen (HLA) DR expression and the extent of the acute-phase response, by determination of white blood cell count and differentiation, plasma interleukin (IL) 6 levels and body temperature in the perioperative period, were examined.

Results: rhGM-CSF treatment minimized postoperative suppression in PHA skin test reactivity and increased the numbers of neutrophils and monocytes while enhancing the expression of HLA-DR in the postoperative period. Additionally, both postoperative plasma IL-6 levels and the incidence of fever tended to be higher in the rhGM-CSF group.

Conclusion: In this pilot study, perioperative administration of low-dose rhGM-CSF stimulated certain immune functions that are normally depressed after operation. The implications for the antitumour responses directly after operation and the formation of liver metastases are currently under investigation.

Paper accepted 3 November 2000

British Journal of Surgery 2001, 88, 539–544

Introduction

For patients diagnosed with colorectal carcinoma, surgery with curative intent is the initial necessary treatment. However, major surgery causes a transient immunosuppression, which has been associated with an enhanced risk of infectious complications and an accelerated outgrowth of distant and local metastases[1–4]. Additionally, viable tumour cells are shed into the portal bloodstream during operation and may invade the liver[5]. Thus, operation-induced immunosuppression could facilitate the outgrowth of occult liver metastases and disseminated tumour cells.

The hypothesis that perioperative adjuvant therapy with recombinant human granulocyte–macrophage colony-stimulating factor (rhGM-CSF) would minimize postoperative immunosuppression in patients with primary colorectal cancer operated on with curative intent was studied.

GM-CSF was chosen for its effects on differentiation, recruitment and activation of monocytes/macrophages and neutrophils[6–9]. Monocytes and resident liver macrophages (Kupffer cells) play an important role in the prevention of

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The Editors have satisfied themselves that all authors contributed significantly to this publication liver metastasis[10]. GM-CSF is capable of enhancing their innate cytotoxicity against human colonic carcinoma cells *in vitro*[11,12] and pretreatment in a rat experimental liver metastasis model reduced tumour outgrowth[13]. Likewise, Hill *et al.*[14] showed that GM-CSF could reduce the outgrowth of pre-established mouse tumours, even when given after laparotomy. In clinical studies, GM-CSF has been shown to exert immune-restoring effects on monocytes in different immunocompromised patients, such as those with metastatic solid tumours, patients undergoing high-dose chemotherapy and those with septic shock[15–17].

Patients and methods

Patient details

In this phase II clinical trial, patients with primary colorectal carcinoma were assigned randomly to perioperative rhGM-CSF treatment or to control treatment with saline. The study was single blind for the patients. Patients were included when operated on with curative intent for colorectal carcinoma, with no sign of distant metastases. A Karnowsky performance score greater than 70 per cent was required. The age was set to a minimum of 18 years and a maximum of 75 years. Both sexes were included. Patients who had undergone previous immunotherapy or chemotherapy were excluded, as well as those who were using immunosuppressive medication at the time of diagnosis, or who were suffering from any autoimmune disease. Written, informed consent was obtained from each patient individually, before treatment, according to the guidelines of the ethics committee of the Academic Hospital, Vrije Universiteit, Amsterdam.

Patients underwent operation on day 0 via a median laparotomy with partial colectomy. Both groups received daily subcutaneous injections from 3 days before until 4 days after operation with either 1 ml saline alone or rhGM-CSF (Leucomax®; Schering-Plough, Maarssen, The Netherlands) 2·8 µg per kg body-weight dissolved in 1 ml saline.

Phytohaemagglutinin skin test

The skin test was performed as described previously by Meijer *et al.*[18]. In short, 0·5 µg purified phytohaemagglutinin (PHA) (Glaxo Wellcome, Raleigh, North Carolina, USA) in 0·1 ml saline was injected intradermally on the volar aspect of the forearm at days −4, +1 and +6. The response was measured as the mean diameter of induration 24 h after injection.

Haematological and immunological changes

Samples of heparinized peripheral blood (lithium heparin – Vacutainer®; Becton Dickinson Europe, Cedex, France) were collected on days −4, 0 (just before operation), +1 and +6. The total white blood cell count (WBC) and specific subpopulations of leucocytes were analysed by means of Sys Mex™ (type SE 9000; Charles Goffin, Tiel, The Netherlands).

Whole blood samples were stained with two fluorescently labelled monoclonal antibodies, anti-CD14 and antihuman leucocyte antigen (HLA) DR (Becton Dickinson, Mountain View, California, USA). Red blood cells were lysed with formic acid and stained cells were fixed with paraformaldehyde using the Q-Prep® procedure (Coulter Electronics, Hialeah, Florida, USA). The labelled cells were analysed on a FACScan (Becton Dickinson). The relative expression (mean fluorescence index) of HLA-DR-positive cells *versus* HLA-DR-negative cells was determined on CD14-positive cells.

Plasma interleukin (IL) 6 concentrations were determined with an enzyme-linked immunosorbent assay kit (Pelikine™ compact human IL-6 ELISA kit; CLB, Amsterdam, The Netherlands). The detection limit was less than 2 pg/ml.

Statistical analysis

Differences between the groups at the different timepoints were analysed by means of the two-sample Mann–Whitney *U* test. Differences within groups were analysed with the Wilcoxon signed rank test for matched pairs. Results are expressed as mean(s.e.m.). Significance was accepted at a two-tailed $P < 0.05$.

Results

Patient details

A total of 18 patients were enrolled in the study and randomly assigned to the rhGM-CSF or control group. Two patients were, however, excluded from the study. One patient refused further injection because of musculoskeletal pain and malaise 15 min after the first rhGM-CSF injection. Another rhGM-CSF-treated patient suffered from a transient ischaemic attack 2 days before operation. Therefore, a total of 16 patients was included (*Table 1*). rhGM-CSF treatment was well tolerated in all patients and, besides minor musculoskeletal pain and general tiredness after the first injection in two patients, no significant side-effects or dermal abnormalities at the injection site were observed.

Postoperative outcome

One patient in the control group experienced anastomotic leakage 6 days after hemicolectomy; the patient underwent reoperation and an ileostomy was constructed. The patient later developed an abscess of the abdominal wound, which was drained. Two months later the stoma was closed successfully and an ileotransverse anastomosis was constructed. Within 1 year this patient was diagnosed with a brain metastasis and received radiation therapy. Another patient developed a local recurrence and distant metastases, and received chemotherapy.

In the rhGM-CSF group one patient was diagnosed with a pulmonary embolus by ventilation–perfusion scanning 5 days after operation, despite heparin prophylaxis. This patient was heparinized and no further complications were reported.

Phytohaemagglutinin skin test

The mean(s.e.m.) induration before operation was comparable in the two groups: 11·9(2·0) and 12·3(1·7) mm in the control and the rhGM-CSF groups respectively (P = 0·72). At day + 1, induration in the control group was less than that in the rhGM-CSF group (4·4(3·1) *versus* 9·0(2·6) mm (95 per cent confidence interval (c.i.) 2·0–7·0 mm); P = 0·01). Six days after operation no differences were found between control and rhGM-CSF groups (10·4(5·7) *versus* 11·9(1·7) mm; P = 0·33).

Table 1 Patient details

	Control	rhGM-CSF
Sex ratio (F : M)	3 : 5	2 : 6
Mean(s.e.m.) age (years)	64·1(3·8)	52·6(4·2)
ASA score (I : II : III)	7 : 0 : 1	7 : 1 : 0
Astler–Coller grade (A : B : C)	0 : 8 : 0	1 : 4 : 3
Tumour site (Co : S : R)	5 : 2 : 1	3 : 4 : 1

rhGM-CSF, recombinant human granulocyte–macrophage colony-stimulating factor; ASA, American Society of Anesthesiologists; Co, colon; S, sigmoid; R, rectum

Haematological changes

On days 0 and + 6 the WBC in the rhGM-CSF group was higher than that in the control group (95 per cent c.i. 4·6–8·9 and 3·0–12·7 respectively; P < 0·01 for both days) (*Table 2*). The leucocytosis in the rhGM-CSF group represented a predominant increase in immature neutrophils. Monocytosis was noted in the rhGM-CSF group on days + 1 and + 6. On day + 1 only, there was a significant difference in monocyte counts between the groups (95 per cent c.i. 0·03–0·94; P = 0·04). Lymphocyte counts differed between the groups on day + 6 (95 per cent c.i. 0·39–1·90; P < 0·01), with the rhGM-CSF group having higher counts than the control group. In both groups T cells accounted for 65 per cent of the total lymphocyte population during the perioperative period.

Human leucocyte antigen DR expression on monocytes

The control and rhGM-CSF group had similar mean (s.e.m.) HLA-DR expression levels (mean fluorescence index) at the start of treatment (23·9(3·2) and 19·4(1·7) respectively; P = 0·44) (*Fig. 1*). HLA-DR expression in the rhGM-CSF group on days 0 and + 1 was significantly higher than that in the control group (95 per cent c.i. 10·0–49·0 and 17·0–43·0 respectively; P < 0·01 for both days). No postoperative decrease in HLA-DR expression on day + 1 was detected in the rhGM-CSF group (P = 0·38 *versus* day 0). The control group, on the other hand, did show a small but significant decrease at day + 1 compared with the pre-

Table 2 Haematological changes in the perioperative period

	Perioperative day	Total WBC	Neutrophils	Eosinophils	Basophils	Monocytes	Lymphocytes
Control	−4	6·84(0·56)	4·63(0·55)	0·11(0·06)	0·08(0·04)	0·67(0·13)	1·48(0·21)
	0	6·44(0·54)	4·32(0·58)	0·20(0·04)	0·03(0·01)	0·50(0·05)	1·16(0·19)
	+1	11·99(0·72)	10·50(1·11)	0·06(0·05)	0·00(0·00)	0·68(0·13)	1·05(0·16)
	+6	7·11(0·50)	4·89(0·49)	0·21(0·05)	0·03(0·01)	0·55(0·07)	1·44(0·24)
rhGM-CSF	−4	6·51(0·71)	4·46(0·82)	0·10(0·03)	0·04(0·01)	0·50(0·04)	1·38(0·14)
	0	13·20(1·54)*	9·05(0·96)*	0·56(0·17)*	0·02(0·02)	0·42(0·14)	1·42(0·16)
	+1	15·70(1·57)	11·78(1·41)	0·43(0·13)*	0·02(0·02)	1·14(0·16)*	1·04(0·23)
	+6	14·99(1·95)*	8·31(1·49)*	1·27(0·33)*	0·00(0·00)	1·03(0·23)	2·54(0·37)*

Values are mean(s.e.m.) × 10^6 cells/ml. HBC, white blood cell count; rhGM-CSF, recombinant human granulocyte–macrophage colony-stimulating factor. *P < 0·05 *versus* control group (two-sample Mann–Whitney U test) operative value ($P < 0.01$). On day +6 no difference in the expression between the groups was observed ($P = 0.72$).

Interleukin 6

Plasma concentration of IL-6 did not differ significantly between the groups on any perioperative day, but the levels on day +1 in rhGM-CSF-treated patients tended to be higher than those in controls (mean(s.e.m.) 116·1(38·4) *versus* 41·1(10·2) pg/ml; $P = 0.23$) (*Fig. 2*).

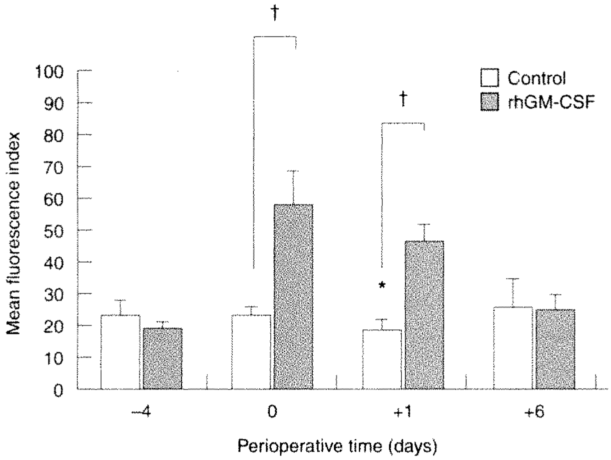

Fig. 1 Human leucocyte antigen DR expression on monocytes at days −4, 0, +1 and +6, expressed as mean(s.e.m.) fluorescence index. rhGM-CSF, recombinant human granulocyte–macrophage colony-stimulating factor. *$P < 0.01$ *versus* control at day 0 (Wilcoxon test); †$P < 0.01$ (Mann–Whitney *U* test)

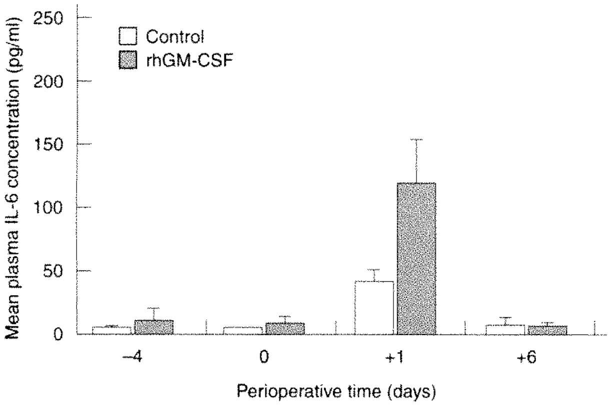

Fig. 2 Mean(s.e.m.) plasma interleukin (IL) 6 levels at days −4, 0, +1 and +6. rhGM-CSF, recombinant human granulocyte-macrophage colony-stimulating factor

Perioperative body temperature

All patients had a normal preoperative body temperature (rhGM-CSF range 37·0–37·5°C, control range 36·4–37·5°C). Postoperative mild fever (38–39°C) was more prevalent in the rhGM-CSF-treated patients than in the control group (six of eight *versus* one of eight; $P = 0.04$, Fisher's exact test). The body temperature of all patients had normalized on day +6.

Discussion

The disappointing 5-year disease-related survival rate of patients diagnosed with colorectal carcinoma is due mainly to the presence of occult liver metastases and/or tumour cell dissemination during operation[5,19]. An alert immune system is necessary to eliminate these tumour cells, but, unfortunately, surgery lessens immune responsiveness. Boosting the immune system in the perioperative period might therefore be of great value. Several groups have performed studies with perioperative interferon α and/or IL-2, and have shown an augmented postoperative natural killer and T-cell function in patients operated on for colorectal carcinoma[20–22]. Additionally, Schafer *et al.*[23] have shown the beneficial effects of perioperative G-CSF on the neutrophil functions of patients undergoing oesophagectomy. In the case of metastatic spread to the liver, however, monocytes and Kupffer cells were also shown to be crucial in the first line of defence[10–13].

In this pilot study, the effect of perioperative rhGM-CSF treatment on the postoperative immunosuppression in patients with colorectal carcinoma operated on with curative intent was evaluated. As the treatment groups were relatively small, no conclusion can be drawn about the effect of rhGM-CSF on postoperative complications and outcome. However, a number of immunological parameters known to correlate with the clinical outcome of the surgical patient and with the capacity to eliminate tumour cells[6–8] were influenced by rhGM-CSF treatment.

The rhGM-CSF-treated patients retained better PHA skin test reactivity after operation. Clinically, decreased delayed-type hypersensitivity skin test reactivity has been shown to correlate with the subsequent development of septic complications and morbidity in severely injured patients[18,24]. Immunologically, suppressed reactivity is an indication of dysfunction in the activation or effector phases of the T-cell response[25]. Thus, rhGM-CSF might improve T-cell responsiveness directly after operation.

rhGM-CSF treatment increased the number of monocytes found immediately after operation until 6 days later. No direct effect of rhGM-CSF on preoperative monocyte counts was detected, probably because of the low treatment dosage[26]. rhGM-CSF induced an increase in monocyte HLA-DR expression, as had been shown previously by Schmid *et al.*[6]. Additionally, the postoperative decrease in HLA-DR expression, normally observed after major trauma[25,27,28], was prevented by rhGM-CSF administration. Reduction in HLA-DR predates, and often predicts, the development of postoperative septic complications[27,28]. The fact that the rhGM-CSF-treated patients possessed more monocytes with higher HLA-DR expression levels in the postoperative period may result in an improved major histocompatibility complex-restricted antigen presentation during this crucial period and a more efficient generation of tumour- and pathogen-specific cytotoxic T cells. An increase in the number of peripheral T cells on day +6 and enhanced PHA skin test reactivity on day +1 was noted in the rhGM-CSF-treated patients.

The leucocytosis seen in the rhGM-CSF group represented an increase in immature neutrophils, as expected[26]. In addition, rhGM-CSF is known to induce activation of neutrophils and eosinophils, leading to an increased oxidative burst and bacterial killing[9]. In the rhGM-CSF treatment group, activated and increased numbers of granulocytes in the perioperative period might reduce postoperative infectious complications. However, no reduction in the incidence of postoperative infections after daily low-dose perioperative rhGM-CSF administration in (mainly) patients with advanced cancer could be found by Meropol *et al.*[29], possibly as a result of the previous chemotherapy or radiotherapy that most of these patients had undergone. In the present study, one patient in the control group and none in the rhGM-CSF group developed infection after operation.

Postoperative IL-6 levels tended to be higher in the rhGM-CSF group. This coincided with a higher body temperature. This might indicate that there was a stronger acute-phase response in these patients[30]. More trauma results in higher IL-6 levels, and high levels after operation are normally an indication of the extent of postoperative stress[25,30]. On the other hand, IL-6 is capable of reducing neutrophil apoptosis and is involved in haematopoiesis, thereby increasing the number of blood neutrophils and haematopoietic progenitor cells after operation[31,32]. A synergistic action with other haematopoietic growth factors, including GM-CSF, has been reported[33], which could explain the mild fever in the rhGM-CSF group.

In conclusion, it seems that perioperative low-dose rhGM-CSF treatment might compensate partly for suppressed immune functions in the postoperative period. Whether there are any consequences for the development of infectious complications and antitumour responses directly after operation is currently under investigation. The value of perioperative rhGM-CSF treatment in the prevention of liver metastases during follow-up should be examined more extensively in a larger clinical setting.

Acknowledgements

The authors thank the Dutch Schering-Plough subsidiary, Maarssen, The Netherlands, for kind provision of rhGM-CSF. They acknowledge E. Broug-Holub for early coordination of the study and J. Visser for the preparation of PHA. For HLA-DR antigen fluorescence activated cell sorting analysis, they thank A. Kromhout from the Department of Pathology and Immunology of the Academic Hospital, Vrije Universiteit, Amsterdam, The Netherlands.

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Decreased tyrosine kinase C expression may reflect developmental abnormalities in Hirschsprung's disease and idiopathic slow-transit constipation

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Background: Some patients with Hirschsprung's disease have refractory constipation following excision of aganglionic bowel, as do patients with idiopathic slow-transit constipation (STC). Gut motility depends on enteric neuronal development in response to expression of trophic factors and their receptors. Recent studies indicate the importance of neurotrophin 3 (NT-3) and its high-affinity receptor tyrosine kinase C (trk C) in enteric neuronal development.
Methods: Blinded quantitative immunohistochemical analysis of colon from patients with Hirschsprung's disease (aganglionic, hypoganglionic and normoganglionic) ($n = 5$), STC ($n = 6$) and appropriate age-matched control tissues ($n = 5$) was performed for NT-3 and trk C. Sural nerve morphometry and immunostaining were undertaken in three patients with STC who had abnormalities on limb autonomic and sensory testing.
Results: A significantly higher proportion of submucous plexus neurones was trk C immunoreactive in control infant than adult colon (mean(s.e.m.) 73(9) *versus* 16(3) per cent of the total; $P < 0.001$), in accord with a role in development. The proportion of submucous plexus trk C-immunoreactive neurones was reduced in colon from patients with Hirschsprung's disease (28(7) per cent of total in normoganglionic Hirschsprung's disease; $P < 0.007$ *versus* infant controls) and STC (10(1) per cent of total; $P = 0.053$ *versus* adult controls). No abnormalities of STC sural nerves were detected by morphometry or immunostaining.
Conclusion: Decreased trk C expression may reflect developmental abnormalities in Hirschsprung's disease and idiopathic STC. Trk C activation by NT-3 or drugs may provide novel treatments.

Presented in abstract form to the Pacific Association of Pediatric Surgeons, Las Vegas, Nevada, USA, May 2000
Paper accepted 23 November 2000 British Journal of Surgery 2001, 88, 545–552

Introduction

It is known that a proportion of patients with Hirschsprung's disease have long-term disturbances of defaecatory function following corrective surgery[1]. Some such children, who continue to complain of refractory constipation, have a measurable delay in colonic transit[1]. A separate group of predominantly female patients has severe constipation also arising in infancy or childhood without the characteristic histological changes of Hirschsprung's disease (i.e. aganglionosis) or colonic dilatation, but with a measurable delay in colonic transit (slow-transit constipation; STC)[2]. These patients, who commonly present in adulthood, may require surgery (colectomy), with highly variable outcomes[3].

Morphological studies of proximal ganglionic tissue from patients with Hirschsprung's disease and colonic tissue from patients with STC have provided some evidence of enteric neuronal abnormalities[4–6], but the aetiology of the motor abnormality in either group of patients remains unclear. Recent studies of the sequential actions of essential growth and transcription factors have revealed that enteric neuronal development involves a complex interaction of lineage-determined and microenvironmental elements.

The genetic signals that are critical for neural crest migration and differentiation have been identified by studying natural and targeted mutations in mice, and include the normal transcription of genes encoding neurotrophins, their receptors and associated neuropoietic cytokines[7–10]. In early development (mouse E12), progenitors of the enteric nervous system (ENS) depend on the correct expression of receptor tyrosine kinase (RET) and glial cell line-derived neurotrophic factor (GDNF) for survival[9]. Later (mouse E14–16), neurotrophin 3 (NT-3) promotes development of glia and neurones and enhances neurite outgrowth, acting via its high-affinity receptor tyrosine kinase C (trk C)[9,10].

The localization of some trophic factors and their receptors has been investigated in developing and postnatal normal human intestine[11,12] and in patients with Hirschsprung's disease[13]. In the present study, the distribution of NT-3 and its high-affinity receptor trk C, and of GDNF and its receptor RET, was examined in the intestine of patients with Hirschsprung's disease or STC. As these factors play a role in the development of other components of the peripheral nervous system[8,14,15] that show subclinical abnormalities in Hirschsprung's disease[16] and STC[17], sural nerve biopsies were also studied from a small number of patients with STC.

Patients and methods

Hirschsprung's disease

Colonic and rectal tissues from five patients, four boys and one girl, aged 0·7–3·1 (median 0·8) years, were studied. All patients had sporadic distal colonic (n = 4) or short-segment (n = 1) disease, without clinical evidence of an established major genetic syndrome, e.g. Down's syndrome or Shah–Waardenburg syndrome. The patients used in the study were not known to suffer from clinically significant refractory constipation, although transit studies had not been performed. Specimens were taken from aganglionic and normoganglionic regions and verified on the basis of histological characterization. The 'transitional zone' (hypoganglionic region) was grossly identified as the area of dilatation proximal to the contracted aganglionic region, and confirmed microscopically by the presence of hypertrophic nerve trunks with a reduced number of ganglia.

Slow-transit constipation

Nine patients with idiopathic STC were studied in total (six colonic tissue studies, three sural nerve studies). All were women, aged 24–73 (median 42) years. All patients had symptomatic evidence of chronic functional constipation as defined by agreed criteria[18]. Median bowel habit was once per 10 days. Delayed colonic transit was demonstrated by radio-opaque marker retention (more than 20 per cent at 100 h) and/or by radioisotope studies (four patients)[19]. Anorectal physiological examination confirmed the presence of the rectoanal inhibitory reflex, but two patients had reduced anal canal squeeze pressures. Small or moderate rectoceles were present in three patients, but all but one patient were able successfully to evacuate the majority of contrast during standard proctography. Seven patients had rectal hyposensation to balloon distension (latex balloon with constant inflation of air at 1 ml/s) compared with the normal range for women aged less than 50 years.

Sigmoid colonic tissue was obtained from six patients, all of whom underwent subtotal colectomy and ileorectal anastomosis. Sural nerve tissue was obtained at the ankle under local anaesthesia from three women with STC (aged 38–62 years) who had no abnormalities on clinical examination, but who had clear deficits in the lower limbs on quantitative sensory and autonomic tests. These quantitative tests[17] had been performed on two occasions by different operators with an interval of greater than 12 (range 14–30) months. Small sensory fibre dysfunction, as evidenced by significantly raised thermal thresholds, in particular to warm perception, was present in all three biopsied patients. One patient also had autonomic dysfunction, as shown by reduced axon-reflex sweating. Such abnormalities were consistently reproduced twice on both separate occasions. Sural nerve neurophysiological studies (conduction velocity, amplitude of sensory action potential) were normal.

Controls

Age-matched control tissues were obtained for Hirschsprung's disease tissues from the colon of infants and children with anal atresia at colostomy sites (*n* = 5; age 0·1–2·7 years). Although not strictly the case, this group has been termed control 'infant'. While it is accepted that the colon proximal to the site of atresia may not be entirely normal in such patients, the availability of infant tissues is limited and necessitated their use. For STC, control colon was obtained from patients undergoing colonic resection for uncomplicated neoplastic disease or familial adenomatous polyposis (*n* = 5; age 26–78 years). Normal sural nerves were obtained from age-matched patients undergoing surgical limb amputations for non-neurological conditions (*n* = 5) for the immunocytochemical studies, and biopsies from organ donor cases without evidence of peripheral neuropathy (*n* = 3) for the morphological studies.

Immunohistochemistry

All intestinal specimens were snap frozen in liquid nitrogen and kept at – 70°C until use. Full-thickness samples of colon were embedded in OCT (Tissue-Tek; R. Lamb, London, UK) to allow transverse frozen sections to be cut as near to perpendicular as possible. Sural nerve was embedded to allow longitudinal frozen sections. Antibodies to neurotrophins, receptors and neurofilaments used in the study are described in *Table 1*. Frozen tissue sections (10 µm) were collected on to poly L-lysine-coated (Sigma, Poole, UK) slides, postfixed in Zamboni fluid (2 per cent w/v formalin, phosphate 0·1 mol/l; 15 per cent v/v saturated picric acid) and washed in phosphate-buffered saline (phosphate 0·1 mol/l, 0·9 per cent w/v saline, pH 7·3) before incubation with primary antibodies. Sites of antibody attachment were detected using a nickel-enhanced, avidin-biotin-complex immunoperoxidase method[20]. Negative control immunostaining included omission of primary antibodies or replacement with normal rabbit serum. Preparations were counterstained for nuclei with either haematoxylin and eosin or 0·1 per cent w/v aqueous neutral red, dehydrated and mounted in a xylene-based mountant (DPX; BDH/Merck, Poole, UK) before photomicrography. Trk C- or NT-3-immunoreactive neurones in the submucous and myenteric plexuses were counted in a minimum of four non-consecutive tissue sections from each region in diseased and normal intestine, and compared with counts of cells in adjacent tissue sections routinely stained (haematoxylin and eosin) or immunostained for neurofilaments. Counts were expressed as a proportion of the total obtained with haematoxylin and eosin or neurofilament staining. The area of immunoreactivity for GDNF, RET and neurofilaments in sural nerve was measured in a minimum of three microscopic fields (final magnification × 100) per section from each case using computerized image analysis (Seescan, Cambridge, UK).

Sural nerve morphometry

The specimens were fixed in 2·5 per cent glutaraldehyde in piperazine-*N*-*N*′-bis(2-ethane sulphonic acid) buffer. Following postosmication and dehydration they were embedded in Durcupan (Agar Scientific, Stansted, UK) via epoxypropane. Semithin sections were stained with thionin and acridine orange. Ultrathin sections were contrasted with uranyl acetate and lead citrate. Myelinated fibre density and size distribution were examined using an IBAS 2 image analyser (Kontron, Eching, Germany). Estimates of unmyelinated axon densities were made on electron micrograph montages at a magnification of × 10 000.

Statistical analysis

Results are expressed as mean(s.e.m). The percentages of immunopositive neuronal cell bodies were compared with the Mann–Whitney U test. $P < 0{\cdot}05$ was taken as significant.

Approval

The studies were approved by the local ethics committee (East London and City Health Authority).

Results

Colonic studies

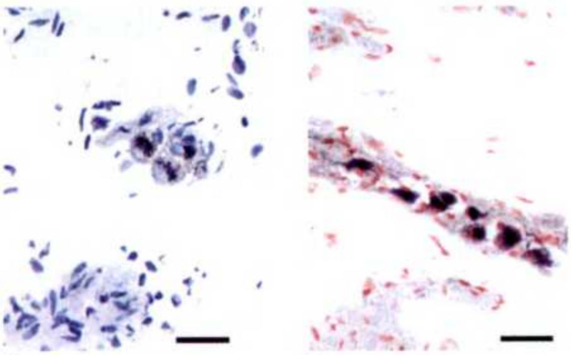
Control tissues

Trk C and NT-3 immunoreactivity was detected in all tissues studied (*Figs 1–3*). The proportion of trk C-immunoreactive neurones in the submucous plexus was higher in control infant than in control adult colon (73(9) *versus* 16(3) per cent of the total; $P < 0{\cdot}001$). A relatively low percentage of neurones was trk C immunoreactive in the myenteric plexus of both infant and adult colon (*Figs 1* and *2*). A similar predominance of NT-3-immunoreactive neurones was observed in the submucous plexus compared with the myenteric plexus of control infant tissues (98(2) per cent in infant submucous plexus *versus* 24(4) per cent in myenteric plexus) (*Figs 1* and *3*). GDNF immunoreactivity and RET immunoreactivity were detected in neural

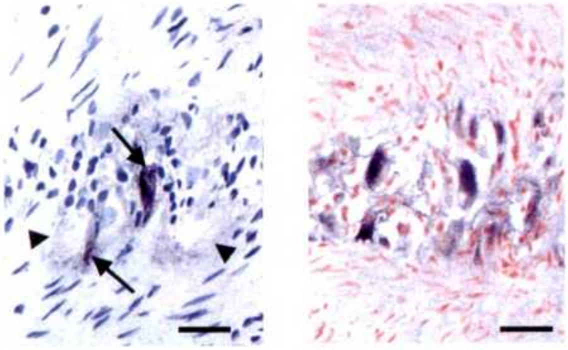
Table 1 Antibody characteristics

Immunogen	Donor species	Source	Dilution
Recombinant human NT-3	Rabbit	Amgen, Thousand Oaks, California, USA	1 : 40 000
GDNF	Rabbit	Autogen Bioclear, Calne, UK	1 : 2000
Trk C	Mouse	Genentech, San Francisco, California, USA	1 : 100
RET	Mouse	Novocastra, Newcastle, UK	1 : 50
Neurofilaments	Mouse	Dako, Ely, UK	1 : 50 000
Peripherin	Mouse	Novocastra, Newcastle, UK	1 : 4000

NT-3, neurotrophin-3; GDNF, glial cell line-derived neurotrophic factor; RET, receptor tyrosine kinase



a Trk C, submucous **c** NT-3, submucous



b Trk C, myenteric **d** NT-3, myenteric

Fig. 1 a, b Trk C and **c, d** neurotrophin 3 (NT-3) immunoreactivity in submucous neurones and myenteric neurones. Neurones are counterstained with either haematoxylin (blue nuclei) or neutral red (red/pink nuclei). Arrows indicate immunopositive cells and arrowheads indicate immunonegative cells. Scale bars, 40 µm

supporting cells and neuronal cells respectively (data not shown).

Hirschsprung's disease and slow-transit constipation

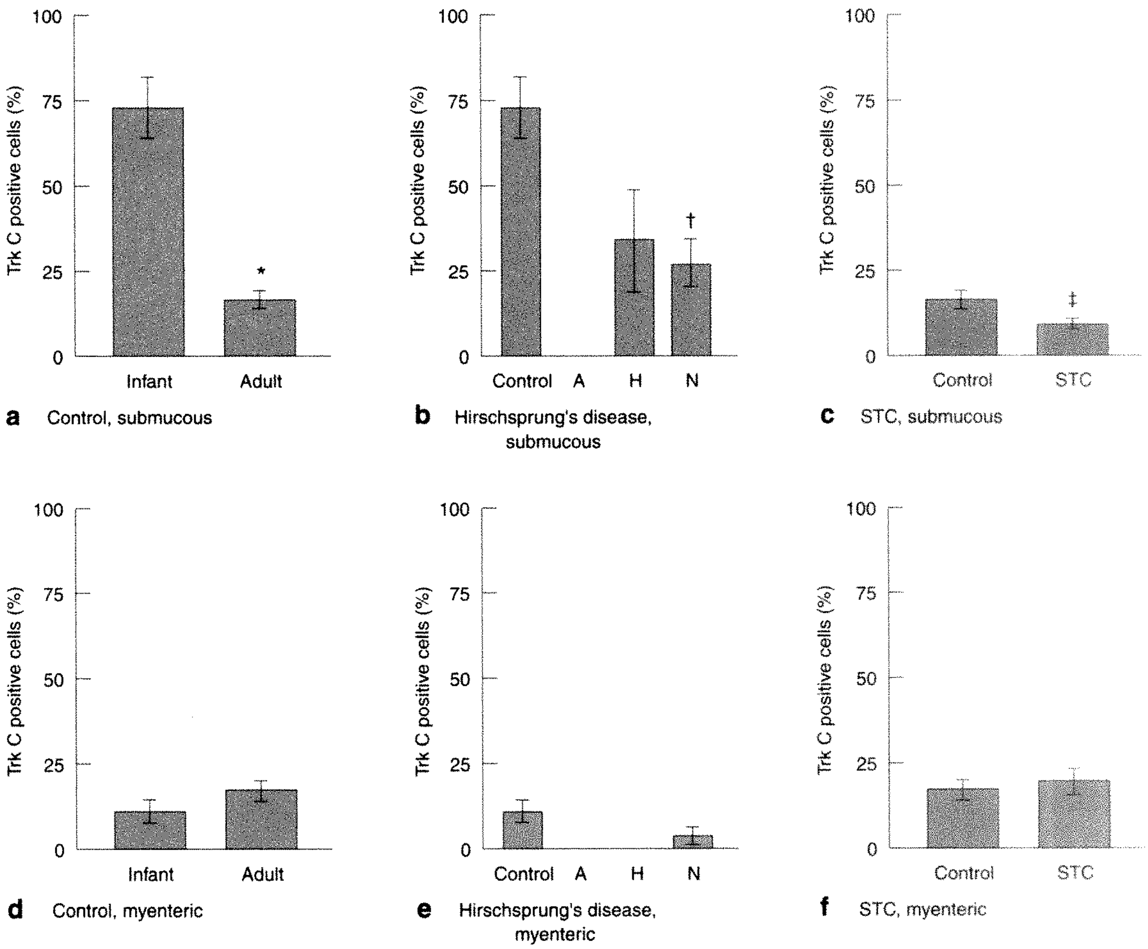
The percentage of trk C-immunoreactive neurones in submucous plexus was significantly reduced in normoganglionic colon from patients with Hirschsprung's disease compared with that in age-matched controls (28(7) per cent in normoganglionic Hirschsprung's disease *versus* 73(9) per cent in control infant; $P < 0{\cdot}007$) (*Fig. 2*). A similar trend was observed for colonic tissue from patients with STC (10(1) per cent for STC *versus* 16(3) per cent for control adult; $P = 0{\cdot}053$) (*Fig. 2*). Few trk C-immunoreactive neurones were seen in the myenteric plexus in tissues from patients with Hirschsprung's disease. NT-3 immunoreactivity was preserved in neurones of the submucosal plexus of normoganglionic Hirschsprung's disease colonic tissues (83(11) per cent), but reduced in hypoganglionic tissues (54(19) *versus* 98(2) per cent in controls; $P = 0{\cdot}025$) (*Fig. 3*). There were no significant changes in NT-3 immunoreactivity (either plexus) in patients with STC compared with controls. GDNF and RET immunoreactivity similarly appeared normal in tissue from patients with normoganglionic Hirschsprung's disease or STC. In Hirschsprung's disease tissues, RET enteric neurone staining was absent in aganglionic segments, but GDNF nerve fibre staining was preserved in hypoganglionic and aganglionic tissues. Measurement of the total number of neurones in control and STC intestine showed no significant difference in either plexus (control *versus* STC: 3·3(1·0) *versus* 2·4(0·4) cells/mm in submucous plexus; 2·7(0·6) *versus* 2·2(0·4) cells/mm in myenteric plexus).

Sural nerve studies

Morphometric analysis of sural nerve biopsies from patients with STC showed normal densities and size distributions for myelinated nerve fibres, and normal densities for unmyelinated axons. These did not differ significantly from published normal ranges[21]. Immunocytochemical studies of sural nerves from patients with STC showed no differences from controls. Antibodies to neurofilaments showed strong staining of large- and small-diameter fibres throughout the nerve in all cases. Antibodies to NT-3 showed a few weakly stained fibres while antibodies to RET or GDNF immunostained a subpopulation of small-diameter fibres in both control nerves and those from patients with STC. Image analysis of sural nerves showed no significant difference between controls and STC in the amount of immunoreactivity for neurofilaments, GDNF or RET (control *versus* STC: 26(3) *versus* 27(3) percentage area immunostaining for neurofilaments; 12(3) *versus* 18(5) per cent for GDNF; 30(4) *versus* 19(5) per cent for RET). Immunostaining with antibodies to peripherin, which recognize a small neurofilament component (57 kDa), also showed no significant change in sural nerves from patients with STC (control *versus* STC: 21(3) *versus* 21(1) percentage area immunostaining). Trk C and NT-3 immunoreactivities were too low to allow image analysis, but on microscopic inspection the degree of immunoreactivity appeared similar.

Discussion

Only in recent years have paediatric surgeons begun to examine critically the long-term functional outcomes after surgery for Hirschsprung's disease in childhood[1]. Although comparison of different series is hampered by age, pattern of disease, length of follow-up, early postoperative complica-



a Control, submucous

b Hirschsprung's disease, submucous

c STC, submucous

d Control, myenteric

e Hirschsprung's disease, myenteric

f STC, myenteric

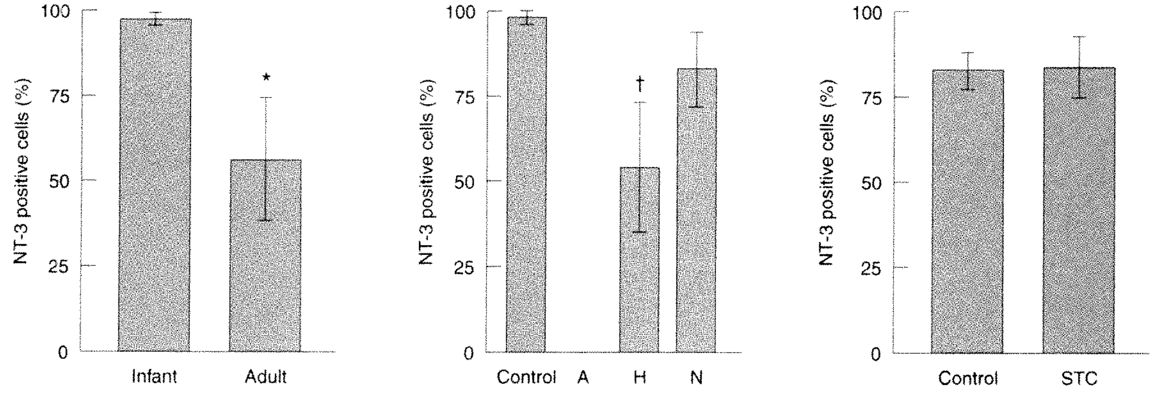
Fig. 2 Mean(s.e.m.) percentage of trk C-immunoreactive submucosal (**a**–**c**) and myenteric (**d**–**f**) neurones in colon from (**a**, **d**) infant and adult controls, (**b**, **e**) patients with Hirschsprung's disease and (**c**, **f**) patients with slow-transit constipation (STC).
A, aganglionic; H, hypoganglionic; N, normoganglionic. $^*P < 0{\cdot}001$, $^\dagger P < 0{\cdot}007$ *versus* infant controls; $^\ddagger P = 0{\cdot}053$ *versus* adult controls (Mann–Whitney *U* test)

tions, and outcome measures used[1], it is generally accepted that refractory constipation occurs in a proportion of patients, regardless of the exact restorative surgical technique used[1]. Motility disturbances in retained histologically normoganglionic regions of intestine have been demonstrated both in anorectal Hirschsprung's disease (abnormal proximal colonic transit)[1] and in total colonic aganglionosis (abnormal oesophageal and duodenal motility)[22]. In the latter, antroduodenal manometric changes were characteristic of a neuropathic process.

STC is a motility disorder defined by the finding of a delay in colonic transit. Manometric testing reveals a reduction in the frequency and amplitude of high-amplitude propagating contractions in the colon[23], and motor abnormalities in the extracolonic gastrointestinal tract and urinary tract. A large proportion of such patients have symptoms that arise in early childhood or infancy, and many report a history of constipation in other family members[24].

Based on alterations in immunoreactivity for a number of neurotransmitters[6] or other neurone-associated antigens[4,5], it has been suggested that an intrinsic myenteric neuronal abnormality might underlie the observed physiological abnormalities in postoperative constipated Hirschsprung's disease, and in patients with STC. The aetiology of such degeneration is not known in either condition. In STC, previously tested hypotheses (laxatives, absorption, hormones, psychological abnormalities, endogenous opioids, etc.) have not provided conclusive results.

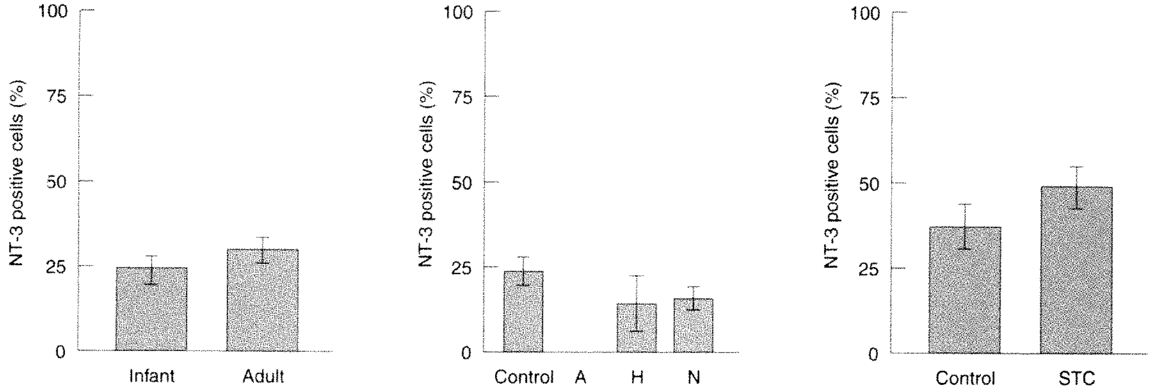
In Hirschsprung's disease, molecular genetic analyses have now identified several, functionally dependent, susceptibility genes in pathways crucial for normal ENS development[25]. Such genomic discoveries have heightened



a Control, submucous

b Hirschsprung's disease, submucous

c STC, submucous



d Control, myenteric

e Hirschsprung's disease, myenteric

f STC, myenteric

Fig. 3 Mean(s.e.m.) percentage of neurotrophin 3 (NT-3)-immunoreactive submucosal (**a**–**c**) and myenteric (**d**–**f**) neurones in colon from (**a**, **d**) infant and adult controls, (**b**, **e**) patients with Hirschsprung's disease and (**c**, **f**) patients with slow-transit constipation (STC). A, aganglionic; H, hypoganglionic; N, normoganglionic. $^*P = 0.039$, $^\dagger P = 0.025$ *versus* infant controls (Mann–Whitney U test)

interest in the functional role of neurotrophins and related factors in the ontogeny of the ENS, and more recently in terms of a postnatal role in plasticity[25]. The progenitors that colonize the bowel below the rostral foregut depend for their survival and/or development upon activation of the RET receptor complex by GDNF[7,15] and other related RET ligands such as neurturin[26]. No enteric neurones develop below the rostral foregut in mice lacking GDNF[27] or RET[7]. Such activation is early (E12), but GDNF and RET continue to be expressed in the ENS and are found in postnatal gut[12]. Previous studies of Hirschsprung's disease tissue have shown absent[28], decreased[29] or normal[12] GDNF levels in aganglionic bowel, with no difference in GDNF immunoreactivity in hypoganglionic bowel[12]. In the present study, the expression of RET and GDNF was normal in ganglionic Hirschsprung's disease and STC tissues, suggesting that these may not be generally involved, at least in some sporadic cases.

Trk C, the high-affinity receptor for NT-3, is expressed by crest-derived cells isolated from foetal bowel[30]. Neurones of the myenteric plexus are increased in both number and size in transgenic mice that overexpress NT-3[31]. While the ENS has been reported to be present in mice with targeted mutations that prevent expression of NT-3[8] or trk C[32], it has not been shown to be entirely normal in these animals. In contrast to GDNF, NT-3 has no effect at E12, but promotes glia/neuronal development, and enhances neurite outgrowth at E14–16[9]. Expression of trk C may itself be regulated by NT-3, as observed in the developing peripheral nervous system. Trk C and NT-3 are co-localized in postnatal human ENS[13] and coexpressed in adult rat ENS[33], suggesting an autocrine role. In the present study, a markedly higher proportion of submucous plexus neurones were trk C immunoreactive in control infant than control adult colon, further supporting a role for trk C/NT-3 in the normal development of the human ENS. In this and a previous study of Hirschsprung's disease, NT-3 was absent in the aganglionic colon and reduced in transitional intestine, whilst trk C was absent only in the aganglionic region[11]. Additionally, in this study, although the overall neuronal architecture in normoganglionic gut tissues of Hirschsprung's disease and STC was normal, the percentage of neurones expressing trk C was reduced in both. There were no significant changes in NT-3-immunoreactive neurones in STC. It may thus be hypothesized that in these cases there is a failure of one or more regional mechanisms that lead to increased phenotypic expression of trk C in ontogeny, which in turn may contribute to altered connectivity or function.

No major morphological or immunocytochemical abnormality was observed in sural nerve biopsies from patients with STC. The minor abnormalities observed were not typical of an acute or ongoing chronic, degenerative process, and this was consistent with the lack of deterioration in detected subclinical quantitative abnormalities. Such abnormalities may therefore be congenital. The relatively minor clinical effects in the limbs and pathological changes in sural nerves in STC suggest that additional factors are involved in development of neural crest-derived tissues in different regions and systems, which deserve further investigation.

The findings in this study suggest that the reduction in trk C receptors in Hirschsprung's disease may account for continuing dysmotility problems after resection of all aganglionic bowel. The abnormality may also be a cause of idiopathic STC, particularly when this starts in childhood. Trk C activation by either its ligand NT-3 or specifically designed drugs may provide an alternative novel therapy for these often resistant diseases. Indeed, recent data indicate that recombinant human NT-3 can accelerate intestinal transit in humans[34].

Acknowledgements

The authors thank R. King and J. Muddle for help with sural nerve morphometry, P. Misra for neurophysiological studies, R. Birch for performing sural nerve biopsies, The Wellcome Trust, UK, for grant support, and the UK/Hong Kong Joint Research Scheme for facilitating the travels of P.K.H.T. and C.H.K.

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Original article

Topical diltiazem ointment in the treatment of chronic anal fissure

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Background: Chronic anal fissure has traditionally been treated surgically. Initial enthusiasm for chemical sphincterotomy has waned because of poor outcomes with glyceryl trinitrate ointment. In this study the use of topical 2 per cent diltiazem ointment has been investigated as an alternative method of chemical sphincterotomy.

Methods: A prospective assessment of 71 consecutive patients with a chronic anal fissure treated with 2 per cent topical diltiazem ointment for a median duration of 9 (range 2–16) weeks was performed.

Results: Fifty-one patients (75 per cent) experienced healing of the fissure after 2–3 months of treatment with topical diltiazem. Seventeen patients who did not heal were treated for a further 8 weeks with topical diltiazem. Eight of these patients subsequently healed with diltiazem. Fifty-nine of 67 patients who completed follow-up therefore healed on diltiazem ointment. Four patients experienced perianal dermatitis and one patient experienced headaches. No other side-effects were recorded. After a median of 32 (range 14–67) weeks' follow-up following completion of treatment, 27 of 41 patients available remain symptom free. Six of seven patients with recurrent fissure were treated successfully by repeat chemical sphincterotomy.

Conclusion: Topical 2 per cent diltiazem ointment used as an agent for chemical sphincterotomy for chronic anal fissure offers significant healing rates but does not have a significant side-effect profile, which may aid compliance to treatment. Early recurrences are common but usually amenable to further chemical sphincterotomy.

Paper accepted 26 November 2000

British Journal of Surgery 2001, 88, 553–556

Introduction

Anal fissure is a common anorectal condition. It is associated with spasm of the internal anal sphincter[1–3], except in postpartum patients[4], and a reduction in mucosal blood flow[5] with delayed or non-healing of the ulcer. The aim of treatment is to improve the blood supply to the ischaemic area to facilitate healing, if necessary, by reducing resting anal pressure, a function of internal anal sphincter activity.

Traditional surgical techniques for treatment include anal dilatation or partial division of the internal sphincter. These procedures permanently lower resting anal pressure and result in healing of the fissure in the majority of patients. Both of these methods may be complicated by permanent incontinence[6,7]. This significant complication has led to a search for alternative therapies for the treatment of chronic anal fissure.

Chemical sphincterotomy has been tried using a variety of novel agents including topical glyceryl trinitrate (GTN)[8–10], calcium channel blockers such as nifedipine[11] or diltiazem[12–14], and botulinum toxin[15]. Although initially promising, topical GTN has recently been described as having disappointing results with significant side-effects[16,17]. Oral nifedipine and diltiazem have been suggested as alternatives but may also have significant side-effects[11–13]. Topical diltiazem has recently been shown to be effective and may not have the same side-effect profile as the oral preparation[12–14].

This study was undertaken to evaluate the efficacy of topical 2 per cent diltiazem ointment in the treatment of chronic anal fissure, to assess recurrence rates and to determine whether recurrent fissures would be amenable to further chemical sphincterotomy.

Patients and methods

Outpatients with chronic anal fissure seen in Newbury and Reading Hospitals, UK, under the care of one colorectal surgeon between January 1999 and January 2000 were studied prospectively. Patients with Crohn's disease were excluded.

Chronic anal fissure was considered to be present if the patient presented with a history of anal pain on defaecation for at least 2 months which had failed to resolve with stool softeners and simple topical agents. Examination typically revealed a fissure with fibres of the internal anal sphincter visible in the base, induration and/or a skin tag.

Seventy-one consecutive patients (36 women) were treated with 2 per cent diltiazem gel (SLA Pharma, Watford, UK). Their median age was 39 (range 12–76) years. Conservative treatment consisting of stool softeners and topical anaesthetic creams from the general practitioner had failed previously in all patients. Six patients had failed to heal previously with topical GTN and one patient had not healed with oral nifedipine. Two other patients had recurrence of the fissure after lateral internal sphincterotomy. Fifty-eight patients had a posterior fissure, nine an anterior fissure and four patients had both an anterior and posterior fissure. One patient had a postpartum fissure. The median duration of symptoms before commencing treatment with diltiazem ointment was 4 (range 2–18) months.

Patients were advised to massage approximately 2·5 cm of 2 per cent diltiazem hydrochloride gel (approximately 8 mg diltiazem) from a standard delivery tube on to the perianal skin but not actually inside the anus, twice daily for 8 weeks. Patients were not prescribed stool softeners or topical analgesic creams for the duration of treatment. A high-fibre diet was encouraged. Healing was defined by resolution of symptoms (anal pain and bleeding) and the absence of a fissure on examination.

Results

Treatment outcomes are summarized in *Fig. 1*. Forty-seven (73 per cent) of 64 patients who attended the first review healed with topical diltiazem. Seven other patients did not attend the first review although four reported complete resolution of their symptoms at telephone interview. One patient was non-compliant and did not wish further treatment. A total of 51 (75 per cent) of 68 patients had therefore healed at first interview.

Seventeen patients who did not heal initially were given the option of either a further course of diltiazem, topical 0·2 per cent GTN ointment or lateral internal sphincterotomy. Of these 17 patients, 12 opted for a further course of topical diltiazem (range 4–8 weeks), of whom eight had healed at second review.

In total, 59 of 66 patients treated with topical diltiazem healed after a median of 9 (range 2–16) weeks of treatment. Two patients did not heal with diltiazem because of non-compliance with treatment and one did not heal because of poor compliance as a result of allergic dermatitis. A total of four patients experienced perianal dermatitis. Three of these four patients nevertheless healed with topical diltiazem. One patient reported headaches with use of topical diltiazem. No other side-effects were reported.

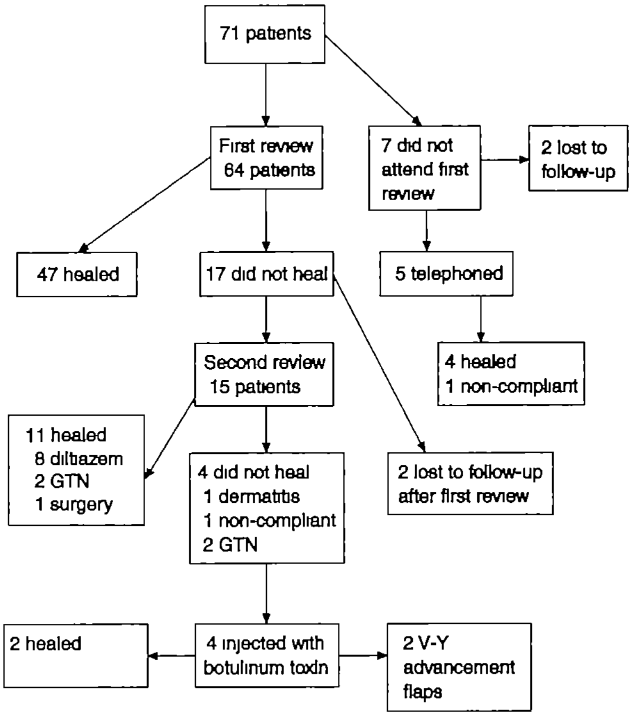

Fig. 1 Outcome after treatment with 2 per cent topical diltiazem. GTN, glyceryl trinitrate

Four patients who failed to heal with diltiazem after an initial 8 weeks of treatment opted to be treated with topical GTN ointment; two healed and one patient elected to undergo surgical sphincterotomy without any further chemical sphincterotomy.

A median follow-up of 32 (range 14–67) weeks is available for 41 of 59 patients who were treated successfully with diltiazem (*Fig. 2*). Twenty-seven of these 41 patients remain asymptomatic. Seven other patients have mild recurrent symptoms without recurrence of the fissure and seven have had a fissure recurrence. Of the seven with a definite recurrence, one patient opted to undergo lateral internal sphincterotomy, three have been treated successfully with topical GTN ointment and three have healed with further topical diltiazem.

A reassessment of the clinical notes and information from the family doctors of the 18 patients who were not available for longer follow-up indicated that no further treatment had been sought.

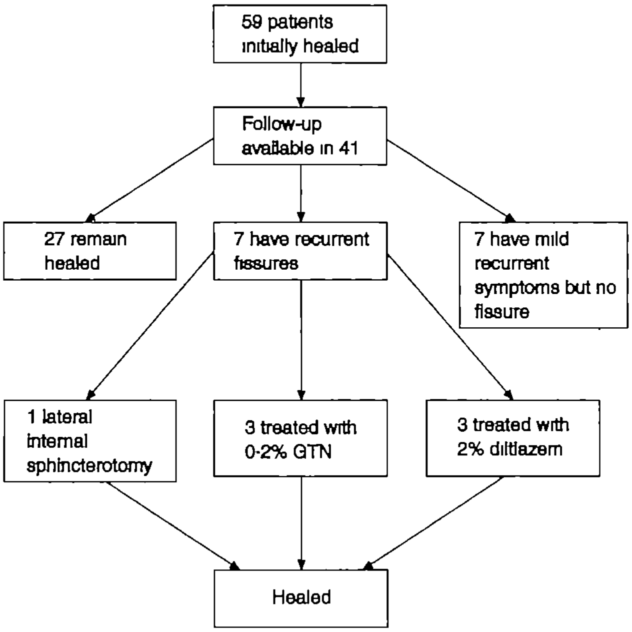
59 patients initially healed
Follow-up available in 41
27 remain healed
7 have recurrent fissures
7 have mild recurrent symptoms but no fissure
1 lateral internal sphincterotomy
3 treated with 0·2% GTN
3 treated with 2% diltiazem
Healed

Fig. 2 Outcome after anal fissure recurrence. GTN, glyceryl trinitrate

Discussion

Chronic anal fissure may be treated by chemical or surgical sphincterotomy at present. Lateral sphincterotomy results in healing for up to 95 per cent of patients but there remains a significant risk of incontinence[6,7].

GTN remains the standard for chemical sphincterotomy against which other newer treatments have to be compared. Within controlled clinical trials, healing with GTN for chronic anal fissure has been achieved in 45–80 per cent of patients[6,8,9,16,17]. However, significant side-effects such as headache, tachyphylaxis and occasional loss of flatus control have been reported[6,8,9,16,17]. A recent uncontrolled study additionally reported poor long-term outcome using GTN, with only 6 per cent of patients healed at 12 months[18].

Research into any 'new' agent for chemical sphincterotomy will therefore have to answer two questions, namely does it work and for how long does it last? Oral calcium channel blockers such as nifedipine and diltiazem have been shown to reduce mean resting anal pressure by between 21 and 28 per cent of healthy volunteers[11,12]. Additionally, healing of fissures has been reported with the use of oral nifedipine[11] and diltiazem[13]. Although changes in diastolic blood pressure are negligible when using oral calcium channel blockers, postural dizziness can occur. The principal side-effects of oral nifedipine or diltiazem are facial flushing and mild headache[12,13].

Topical diltiazem is associated with fewer side-effects, perhaps owing to minimal systemic absorption. Anal pressure was not measured in this study although a reduction in mean resting anal pressure of between 22 and 28 per cent in healthy volunteers and in patients with chronic fissure has been demonstrated previously[12–14]. Dose–response studies have reported that the concentration of 2 per cent is capable of reducing anal pressure without causing significant side-effects[12].

A healing rate of 67 per cent at 2–3 months is similar to that in the more favourable reports on topical GTN but without the troublesome side-effects. A second 8-week course of treatment for those who had not completely healed after the first course resulted in resolution of symptoms in 59 of 66 patients (89 per cent). Non-compliance was uncommon; only four patients (6 per cent) discontinued treatment, one because of perianal dermatitis.

The follow-up available after successful treatment with diltiazem ointment is short and therefore no long-term conclusions can be drawn. One of the drawbacks of chemical sphincterotomy with GTN has been the high fissure recurrence rate. In the present study, after a median of 32 weeks of follow-up, 27 of 41 patients reported themselves to be symptom free. Longer follow-up will nevertheless be required. All but one of the patients with a recurrence were treated successfully by further chemical sphincterotomy.

In conclusion, topical 2 per cent diltiazem appears to be a well tolerated method of chemical sphincterotomy for chronic anal fissure. Prospective randomized trials are required to evaluate it in comparison to topical GTN. Long-term follow-up is also needed to assess the risk of recurrent fissure after initial healing with diltiazem.

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Original article

Expression of the *RET* proto-oncogene in papillary thyroid carcinoma and its correlation with clinical outcome

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Background: In papillary thyroid carcinoma (PTC), presence of the oncogenes *RET/PTC* has been described, but their correlation with prognosis is debated. The aim of this study was to investigate the expression of the *RET* proto-oncogene (*RET*) and correlate it with clinical outcome.
Methods: Sixty-one PTCs were analysed for expression of *RET* and the oncogenes *RET/PTC1–4* by polymerase chain reaction of complementary DNA.
Results: Twenty-nine PTCs (48 per cent) expressed the *RET* tyrosine kinase domain (*RET*-TK). Twelve expressed wild-type *RET* (WT-*RET*). One tumour expressed *RET/PTC3*, one a variant of *RET/PTC3*, and one *RET/PTC1* and WT-*RET* simultaneously. The remaining 14 expressed *RET*-TK only. WT-*RET* expression was detected more frequently in poorly differentiated PTCs ($P < 0{\cdot}05$) and in PTCs from patients with aggressive disease ($P < 0{\cdot}01$). WT-*RET* expression remained an independently significant risk factor for aggressive disease when analysed together with other recognized risk factors using a stepwise multiple logistic regression model.
Conclusion: Almost half of the PTCs showed *RET*-TK expression; in only three was this explained by expression of a *RET/PTC* rearrangement. Instead, expression of WT-*RET* was detected in 45 per cent of the *RET*-TK-positive tumours and this expression was an independently significant risk factor for aggressive PTC.

Presented in abstract form to the Millennium Meeting of Endocrine Surgeons held by the American Association of Endocrine Surgeons, British Association of Endocrine Surgeons and Swedish Association of Endocrine Surgeons, London, UK, May 2000
Paper accepted 24 November 2000
British Journal of Surgery 2001, **88**, 557–563

Introduction

Papillary thyroid carcinoma (PTC) is the most common form of thyroid malignancy. The prognosis is usually excellent with long-term survival rates of more than 90 per cent[1]. However, some tumours behave more aggressively with recurrences and distant metastases. Several prognostic scoring systems (Tumour Node Metastasis, AMES, AGES, MACIS) are currently used to try to predict the prognosis[2–5]. Poor prognosis usually refers to patients aged 40 years or more at the time of diagnosis, local invasiveness and the presence of distant metastases[1]. In addition, the tall cell variant of PTC has been claimed to be more aggressive[6]. The frequent finding of local lymph node involvement at the time of diagnosis is not associated with a poorer prognosis. In spite of the application of prognostic scoring systems, the behaviour of a PTC cannot always be anticipated from its initial clinical features. There is a need to develop additional diagnostic and prognostic markers for preoperative identification of patients with a less favourable prognosis.

The pathogenesis of PTC is associated with previous exposure to ionizing radiation[7] and, in addition, a familial component is evident in approximately 6 per cent of cases[8]. Several genes have been implicated in the molecular carcinogenesis of PTC, including *TP53*, *p21*, *met*, *trk* and *ras*[9,10]. The most commonly described genetic changes in PTCs are the rearrangements of the *RET* proto-oncogene (*RET*), found exclusively in PTC[11], and designated the

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The Editors have satisfied themselves that all authors have contributed significantly to this publication

RET/PTC oncogenes. The wild-type of *RET* (WT-*RET*) induces PTC-like tumours in transgenic mice when expressed constitutionally as the oncogene *RET/PTC*[12]. *RET* encodes a cell membrane-bound receptor tyrosine kinase and the *RET/PTC* oncogenes arise as a result of the fusion of the *RET* tyrosine kinase domain (*RET*-TK) with different unrelated 5′ sequences[13]. Three main forms of rearrangement have been described to date. In *RET/PTC1* and *RET/PTC3* the tyrosine kinase domain fuses with the genes *H4* and *ELE1* respectively[14,15]. *RET/PTC2* arises from a chromosome 10/17 translocation[16]. Other rearrangements have been described in a few cases[17–21] (*Fig. 1*).

The reported prevalence of *RET/PTC* expression in PTC varies considerably, from 5 to 84 per cent[22–30]. Although *RET/PTC* rearrangements may not be present, around 40–70 per cent of PTCs still express *RET*-TK[27–29,31]. Follicular thyroid cells do not normally express *RET*[32], but expression of WT-*RET* was recently detected in PTC[33]. The clinical relevance of *RET/PTC* expression in PTCs is debated[22–26,34,35] and, so far, no correlation between expression of *RET*-TK or WT-*RET* and clinical variables has been established[29,31].

In the present study 61 PTCs were evaluated for expression of *RET*-TK, the common specific rearrangements *RET/PTC1–4* and for WT-*RET*. The genetic findings were then compared with the patients' clinical outcome and with individual clinical and histopathological variables.

Patients and methods

Patients and tumours

Sixty-one PTCs from 61 adult patients were divided into four groups. Group 1 included patients who died from the disease, patients with persistent disease in spite of therapy, and patients with distant metastases that were either present at diagnosis or developed during the course of the disease. These patients were classified as having aggressive PTC disease. Group 2 included patients with lymph node involvement and group 3 included patients without signs of lymph node metastases at the time of operation. The patients in these two groups showed no signs of recurrence or distant spread during follow-up. Group 4 included patients with lymph node involvement but who also had one

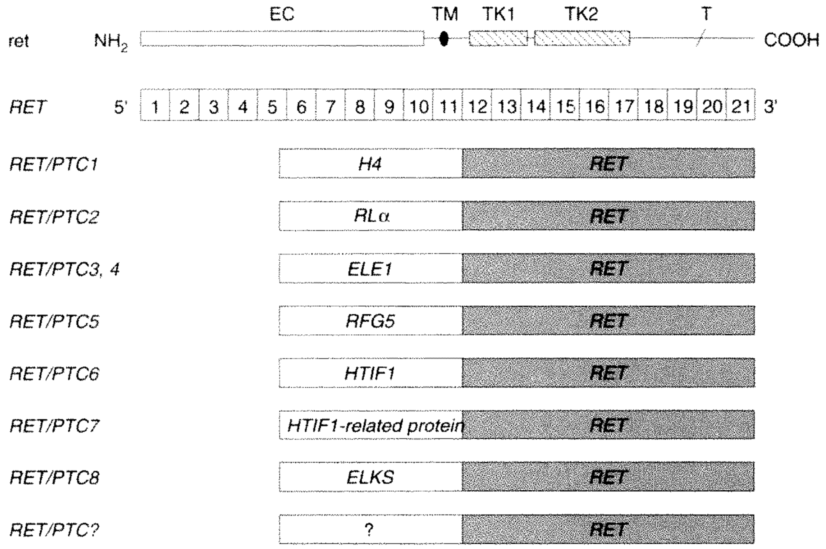

Fig. 1 Schematic representation of the 21 exons encoding the *RET* proto-oncogene (second from top) and its relationship to the ret protein (top). Different regions of the ret protein (EC, extracellular part; TM, transmembrane domain; TK1 and 2, tyrosine kinase domains) are pictured in relation to their encoding exons. The carboxy tail (T) consists of either intron 19 or exons 20 or 21 owing to alternative splicing. The different *RET/PTC* oncogenes (*RET/PTC1–8*) are illustrated schematically at their gene level. Foreign sequences included in these oncogenes are illustrated and named in the left boxes. A breakpoint occurs between exons 11 and 12 and the right boxes (shaded) show the tyrosine kinase domain of the *RET* proto-oncogene. The *ELE1* gene is involved in both *RET/PTC3* and *RET/PTC4* and in some splice variants of these oncogenes. The *HTIF1* and *HTIF1-related protein* genes are involved in *RET/PTC6* and *RET/PTC7* respectively. The question mark indicates possible uncharacterized sequences that may fuse to the tyrosine kinase domain of *RET* resulting in new rearrangements

local recurrence. The recurrences were treated successfully and the patients had no signs of distant spread or further recurrence thereafter (*Table 1*).

In addition, 30 randomly selected patients with follicular thyroid tumours, five carcinomas (FTC) and 25 adenomas (FTA) were included in the study as a reference group. A medullary thyroid tumour was used as a positive control for *RET* expression. A PTC cell line, TPC-1, containing the *RET/PTC*1 rearrangement, together with the cloned vectors containing *RET/PTC*2 and *RET/PTC*3 complementary DNA (cDNA) were used as positive controls for the expression of the different rearrangements.

The tumours were snap frozen in liquid nitrogen at the time of thyroidectomy and stored at – 70°C. The diagnosis of PTC, FTC and FTA was based on the World Health Organization classification[36] and the criteria for poor differentiation were those described by the Armed Forces Institute of Pathology[37]. The MACIS prognostic score[5] was calculated for each patient: less than 7, 20-year specific survival 89 per cent or greater; 7 or more, 20-year specific survival 56 per cent or less. Recurrent disease was defined as reoccurrence of PTC in patients in whom an initial postoperative iodine scan and thyroglobulin measurements had been negative. Patients who were alive with disease, or died from intercurrent disease but with PTC, were considered to have persistent disease.

Table 1 Clinical variables and histopathological data on 61 patients with papillary thyroid carcinoma analysed for *RET* expression

	Group 1 ($n = 14$)	Group 2 ($n = 24$)	Group 3 ($n = 14$)	Group 4 ($n = 9$)
Clinical data				
Sex ratio (M : F)	5 : 9	9 : 15	2 : 12	4 : 5
Mean age (years)	57·2	51·8	54·1	51·5
Mean tumour size (mm)	38	34	22	29
Lymph node involvement	14	24	0	9
Distant metastases	10	0	0	0
Local invasiveness	9	7	2	3
MACIS score*				
< 7	2	20	14	7
≥ 7	12	4	0	2
Clinical outcome				
DFD	5			
DWD	4			
AWD	4			
Alive	1	24	14	9†
Mean follow-up (years)	9·6	3·6	5·8	10·6
History of radiation	0	1	2	1
Histopathological data				
Poorly differentiated	5	1	0	1
Tall cell variant	2	2	3	1

*Reference 5. DFD, dead from disease; DWD, dead from intercurrent disease, but with signs of PTC; AWD, alive with disease; Alive, alive with no signs of PTC or dead from intercurrent disease but with no signs of PTC; †patients with one local recurrence but after treatment alive with no signs of distant spread or dead from intercurrent disease but with no signs of PTC

Methods

Total RNA was extracted using the Ultraspec-II RNA isolation system (Biotecx Laboratories, Houston, Texas, USA). cDNA was synthesized from the RNA by reverse transcription performed at 37°C with random hexanucleotide primers, using the First-strand cDNA Synthesis Kit (Amersham Pharmacia Biotech, Uppsala, Sweden). PCR was performed using 1 µg of cDNA from each tumour as a template. Initial denaturation at 95°C for 5 min was followed by 40 cycles of denaturation at 94°C for 1 min, annealing at 55–63°C for 1 min and extension at 72°C for 1 min, and then completed with a final elongation at 72°C for 10 min. Polymerase chain reaction (PCR) using primers for the *RET*-TK domain (in exons 12 and 13, and in exons 15 and 17), and primers for the specific rearrangements *RET/PTC1–4*, was performed on all PTCs. PCR with primers in exons 11 and 13, spanning the regular breakpoint for the *RET/PTC* rearrangements, was also performed on all PTCs. In eight tumours, which expressed exons 11–13, and in one tumour negative for expression of exons 11–13, the PCR was extended with primers in exons 6 and 8, located in the extracellular part of *RET*. In addition, PCR using primers for *RET*-TK was performed on the five FTCs and 25 FTAs. Negative controls, with no cDNA, were included in all reactions. Integrity of the cDNA was confirmed in all samples using primers for either *GAPDH* or *β_2-microglobulin*. To exclude *RET* expression from C-cells present in the specimens, screening for calcitonin messenger RNA (mRNA) expression was performed in all samples. (Information on primer sequences is available upon request.)

The specificity of the PCR products was confirmed by restriction enzyme digestion using *Bcl*-1 (exons 15–17) and *Taq*-1 (exons 12–13 and 11–13). All samples with PCR products indicating the presence of a *RET* rearrangement were sequenced with an automated sequencer (ABI Prism model 377; Perkin Elmer, Foster City, California, USA).

Statistical analysis

χ^2 and Fisher's exact tests (SPSS for Windows; SPSS, Chicago, Illinois, USA) were used to correlate clinical variables (age 40 years or more, lymph node involvement, extrathyroidal growth, distant metastases, aggressive disease, MACIS prognostic score, poor differentiation and tall cell variant of PTC) with expression of the various *RET/PTC* rearrangements, the expression of *RET*-TK, and the expression of *RET*-TK exons together with exons upstream of the regular breakpoint for the rearrangements.

The association between aggressive disease and the expression of *RET*-TK exons 11–13 obtained from the above analysis was then put into a stepwise multiple logistic regression model to determine whether or not this was an independently significant risk factor[38].

Results

Patients and clinical outcome

Fourteen of the 61 patients with PTC included in this study were considered to have an aggressive disease and were included in group 1. Ten of these patients had distant metastases that were either located in the lung (six patients), in the skeleton (two), in both lung and skeleton (one) or in the abdomen (one). Of the remaining four patients, two died from a locally aggressive PTC and one had persisting local PTC for 6 years but died from intercurrent disease. One patient is still alive after 6 years with locally recurrent tumour, in spite of repeated therapy with surgery and external irradiation.

Thirty-eight patients showed no signs of distant spread or recurrent disease during follow-up. Of these, 24 patients presented with local lymph node spread (group 2) while 14 had no signs of lymph node involvement at the time of operation (group 3). Nine patients had local lymph node involvement and also developed one local recurrence at a median time of 6 years after the first operation (group 4). The recurrences were all treated successfully and the patients were alive at the time of writing with no signs of PTC. Of the 61 patients investigated, eight had the tall cell variant of PTC and seven tumours were classified as poorly differentiated. Data are summarized in *Table 1*.

Table 2 Results of *RET* expression analysis in 61 patients operated on for papillary thyroid carcinoma and grouped according to clinical outcome

	Group 1 ($n = 14$)	Group 2 ($n = 24$)	Group 3 ($n = 14$)	Group 4 ($n = 9$)	Total ($n = 61$)
RET-TK	10	14	3	2	29
WT-*RET*	7	5*	1	0	13*
RET/PTC	1†	2‡	0	0	3
RET-TK only	2	8	2	2	14

RET-TK, *RET* tyrosine kinase domain; WT-*RET*, wild-type *RET*; *RET/PTC*, any of the oncogenes *RET/PTC1–4*. *One patient expressed WT-*RET* and *RET/PTC1* simultaneously; †*RET/PTC3* variant[17]; ‡one *RET/PTC1* and one *RET/PTC3*

Expression of *RET* and *RET/PTC1–4*

RET-TK mRNA expression was detected in 29 of the 61 PTCs (*Table 2*), when primers in exons 15 and 17, and in exons 12 and 13, were used. In 13 of the PTCs *RET*-TK expression was found together with expression of exons 11–13, located on both sides of the regular breakpoint for *RET/PTC* rearrangements (*Fig. 2*). Eight of the nine tumours tested for expression of exons 6–8 were positive, all of which were also positive for exons 11–13. The ninth, negative for exons 6–8, was also negative for exons 11–13.

Three *RET/PTC* rearrangements were found in the 29 tumours expressing *RET*-TK: one *RET/PTC1*, one *RET/PTC3*, and one a rare variant of *RET/PTC3*, described previously only in three patients from Belarus[17]. The rearrangements were confirmed by sequencing the PCR product. No tumours contained the *RET/PTC2* or *RET/PTC4* rearrangement. In the *RET/PTC1*-positive tumour, expression of *RET*-TK, together with exons upstream of the regular breakpoint for the rearrangements, was detected simultaneously. Altogether, 14 tumours expressed *RET*-TK but not exons 11–13 or *RET/PTC1–4*. No tumour expressed calcitonin mRNA. *RET*-TK expression could not be detected in any FTC or FTA.

Correlation between clinical data, histopathological variables and *RET* expression

The number of patients expressing *RET*-TK together with exons upstream of the regular breakpoint for the rearrange-

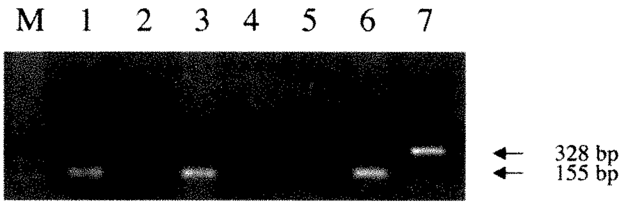

Fig. 2 Polymerase chain reaction products on an agarose gel. Lanes 1 and 2 show a tumour that is positive for *RET* tyrosine kinase (*RET*-TK) exons 15–17 (also for exons 12–13, not shown) and exons 11–13 (upstream of the regular breakpoint for the rearrangements), thus expressing wild-type *RET*. Lanes 3 and 4 show a tumour that is positive for *RET*-TK exons 15–17 (also for exons 12–13, not shown), but not for exons 11–13, and is also negative for *RET/PTC1–4* (not shown), so may contain an unidentified rearrangement. The expected product sizes are 155 bp for exons 15–17 and 328 bp for exons 11–13, shown by the positive controls (using complementary DNA from a medullary thyroid carcinoma) in lanes 6 and 7 respectively. Lane 5 is a negative control. The molecular marker in lane M contains 5 mg of 123-bp DNA ladder

ments was significantly increased in group 1 (seven of 14 *versus* six of 47; $P < 0.01$). Furthermore, poorly differentiated tumours more frequently expressed *RET*-TK together with exons upstream of the regular breakpoint for the rearrangements than well differentiated tumours (four of seven *versus* nine of 54; $P < 0.05$). When analysed together with other recognized risk factors for aggressive disease (age 40 years or more, tumour size greater than 40 mm, poor differentiation, infiltrative growth, tall cell variant of PTC) using a stepwise multiple logistic regression model, expression of *RET*-TK together with exons upstream of the regular breakpoint for the rearrangements was found to be an independently significant risk factor for aggressive disease ($P = 0.042$; odds ratio (OR) 5·5 (95 per cent confidence interval 1·0–30·3)). In this analysis poor differentiation ($P = 0.004$; OR 9·1 (1·1–75·6)) and tumour size greater than 40 mm ($P = 0.002$; OR 9·9 (1·9–50·4)) were also independently significant risk factors for aggressive disease. The difference in WT-*RET* expression between patients with a MACIS score of 7 or more, or less than 7 (seven of 18 *versus* six of 43) was significant ($P = 0.04$).

RET-TK expression, regardless of mechanism, was found in ten of 14 tumours from patients with aggressive disease (group 1), compared with 19 of 47 tumours from patients in groups 2–4 ($P = 0.06$). Seven of ten tumours from patients with distant metastases showed *RET-TK* expression, compared with 22 of 51 tumours from those without distant metastases. Sixteen of 33 tumours from patients with local lymph node spread (groups 2 and 4) expressed *RET*-TK, compared with three of 14 tumours from those without signs of lymph node involvement (group 3). Neither of these two differences was significant. No *RET* expression could be correlated with recurrent disease, extrathyroidal growth or the tall cell variant of PTC. No correlation could be established between any of the *RET/PTC* rearrangements and the above-mentioned variables.

Discussion

Expression of the *RET* proto-oncogene is normally restricted to cells of neural crest origin. In thyroid follicular cells *RET* can be activated by chromosomal rearrangements. In the rearrangements *RET*-TK fuses with different unrelated genes, which are normally expressed in thyroid follicular cells, resulting in the oncogenes *RET/PTC*. This leads to constitutive activation of *RET*-TK function. In all known rearrangements the genetic breakpoint is located in intron 11 of *RET*, so *RET*-TK is involved in all rearrangements[39] (*Fig. 1*).

In this study, almost half of the tumours expressed *RET*-TK, which was due to a known *RET/PTC* rearrangement in three cases only. This discrepancy, also reported by others[27–29], has at least four possible explanations: the presence of still uncharacterized rearrangements, expression of WT-*RET*, illegitimate mRNA transcription and ‘contamination’ of C-cells in the tumour tissue.

The 14 tumours expressing *RET*-TK but no exons upstream of the regular breakpoint for the rearrangements, could contain not yet identified rearrangements. The role of chromosomal rearrangements in tumorigenesis is well established, especially in haematopoietic malignancies, but why two genes from remote chromosomal loci are joined together is still not clear. Different tumour-promoting factors might cause many DNA strand breaks but only those that provide the cell with a growth advantage will show up in a tumour. The growing collection of *RET* rearrangements in PTC[17–21] suggests that several more different rearrangements may be expected.

The tumours expressing *RET*-TK together with upstream mRNA most probably express full-length WT-*RET*. Detection of WT-*RET* mRNA as well as staining of ret protein located to the cell membrane (rearranged ret is cytoplasmic) was recently described in PTC[33]. This suggests a role for WT-*RET* in PTC formation. Overexpression of WT-*RET* could be due to gene amplification, but preliminary data show no copy number alterations on chromosome 10q using comparative genomic hybridization (P. Kjellman, S. Lagercrantz, A. Höög, G. Wallin, C. Larsson, J. Zedenius, unpublished results). It could also be due to activating point mutations in the gene or in its promoter.

If the *RET* expression was due to illegitimate transcription one would expect detection of *RET* mRNA in a larger number of samples. For instance, no FTC or FTA showed any sign of *RET* expression. The detection of *RET*-TK was not due to the presence of C-cells in the tumour samples as screening for expression of calcitonin was negative in all samples.

Only three (5 per cent) of 61 tumours contained a known *RET/PTC* rearrangement, which is less than that in some reports[24–26,30] but similar to others[22,23,29]. The variant of *RET/PTC3* found in one of these patients has been described previously only in three patients from Belarus[17] with a history of radiation. The patient harbouring this rearrangement had no history of radiation. At age 27 years the patient was diagnosed with PTC infiltrating surrounding tissue together with lung metastases. The patient still had signs of active disease at 8 years' follow-up. The fact that one tumour showed simultaneous WT-*RET* and *RET/PTC1* expression probably reflects subclonal growth within a tumour.

RET/PTC rearrangements have been associated with young age and previous exposure to ionizing radiation[7], but the correlation with clinical outcome is controversial. Some have found *RET/PTC* expression more often in patients with small, well differentiated and clinically indolent tumours[23–26], while others suggest a correlation between *RET/PTC* expression and metastatic[22,34,40] or locally invasive[35] PTC. It was not possible to correlate any clinical or histopathological variables to any of the *RET/PTC* rearrangements as they were too few. However, one of the three patients with a *RET/PTC* rearrangement had disseminated disease with lung metastases, indicating that *RET/PTC* rearrangements are not restricted to clinically indolent tumours.

WT-*RET* was expressed more often in tumours from patients with a less favourable clinical outcome (group 1) and in poorly differentiated tumours. Whether this WT-*RET* expression is part of a stepwise progression towards a more aggressive PTC, or results from the dedifferentiation process *per se* is not clear. Still, WT-*RET* expression remained a significant risk factor for aggressive disease independently of tumour differentiation. The association between MACIS prognostic score (describing mortality rate only) and WT-*RET* expression was also significant ($P = 0{\cdot}04$). This suggests that clinical and genetic prognostic markers may be complementary.

Aggressive PTCs showed a tendency to express more *RET*-TK than other PTCs, although this was not significant ($P = 0{\cdot}06$). *RET* expression was not more frequent in the tall cell variant of PTC, which has been stated to be more aggressive. In fact, the tall cell variant of PTC was not over-represented in patients with poor clinical outcome.

WT-*RET* expression was found to be an independently significant risk factor for aggressive PTC disease. It is too early to include *RET* expression as a prognostic marker in the clinical context, but if the correlation between *RET* expression and a less favourable outcome holds true in larger samples, it could be used as an additional marker to identify patients with PTC who could benefit from more extensive treatment.

Acknowledgements

This study was supported by grants from the Swedish Cancer Foundation, the Cancer Society in Stockholm, the Torsten and Ragnar Söderberg and the Fredrik and Ingrid Thuring Foundations, the Swedish Medical Research Council and the National Health and Medical Research Council of Australia.

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Original article

Expression of gastrin in developing gastric adenocarcinoma

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Background: A stepwise progression through premalignant stages has been identified for the intestinal type of gastric carcinoma. As gastrin has been identified as a growth factor for the intestinal type of gastric adenocarcinoma, the aim of this study was to investigate whether gastrin is expressed in premalignant gastric conditions.
Methods: Ninety archival samples of atrophic gastritis, intestinal metaplasia, mild gastric epithelial dysplasia, moderate gastric epithelial dysplasia, severe gastric epithelial dysplasia and intestinal-type gastric adenocarcinoma were obtained. Immunocytochemistry was performed using antibodies directed against gastrin and its post-translational precursors, and the gastrin/cholecystokinin B receptor. Positive staining was identified using the avidin–biotin immunoperoxidase method and quantified using an image analysis system.
Results: Gastrin and its receptor were shown to be expressed in specimens of atrophic gastritis, intestinal metaplasia, epithelial dysplasia and the intestinal type of gastric carcinoma.
Conclusion: Gastrin seems to be an important growth factor in gastric carcinogenesis.

Paper accepted 30 October 2000

British Journal of Surgery 2001, 88, 564–568

Introduction

Gastric cancer is the second most frequent cause of cancer death in both sexes worldwide, with a total number of deaths per year of 628 000[1]. To improve diagnosis and treatment, and reduce the number of deaths, a better understanding of the pathogenesis and biology of the disease is required[2]. Histogenetically, gastric cancers have been classified into two histological types by Lauren: diffuse and intestinal[3]. For the intestinal type of gastric carcinoma a stepwise process of carcinogenesis has been proposed by Correa[4]. It is hypothesized that prolonged *Helicobacter pylori* infection leads to atrophic gastritis. Further mutational events lead to the development of intestinal metaplasia, epithelial dysplasia and finally carcinoma. For diffuse-type gastric carcinoma no such precursor lesions have been identified and *H. pylori* infection is not implicated in its aetiology.

Gastrin is a peptide hormone produced by the G cells of the gastric antrum[5]. It has several physiological functions. It is the principal hormonal stimulant of gastric acid secretion[6] and also a growth factor for parietal, enterochromaffin and mucous cells of the gastric epithelium[7–9]. These physiological actions are mediated via its receptor, the gastrin/cholecystokinin B (CCKB) receptor.

As well as being a growth factor for normal gastric epithelium, gastrin is now accepted as a trophic factor for gastric adenocarcinoma. The gastrin gene is activated in gastric adenocarcinoma cells[10,11], which leads to the production of mature amidated gastrin and the immature forms progastrin and glycine-extended gastrin. All of these species have a proliferative effect[12–16].

Expression of gastrin by gastric premalignant lesions and its role in the progression to malignancy is unknown. The aim of this study was to identify whether gastric premalignant lesions express gastrin and the CCKB receptor. Their expression may suggest the presence of a functional autocrine pathway.

Materials and methods

Formalin-fixed samples of normal gastric fundus and antrum, atrophic gastritis, intestinal metaplasia, mild, moderate and severe epithelial dysplasia, and intestinal-type gastric adenocarcinoma were obtained from the pathology archives ($n = 15$ per condition). These were grouped using the revised Sydney classification by a consultant histopathologist.

Normal gastric antrum and fundus mucosae were used as positive controls for gastrin expression (in G cells) and gastrin/CCKB receptor expression (in entero-chromaffin-like and parietal cells).

Paraffin-embedded sections (4 µm) were placed on 2 per cent 3-aminopropyltriethoxysilane-coated slides; four sections of each specimen were cut. The sections were deparaffinized in xylene and rehydrated in alcohol. Endogenous peroxidase activity was quenched by a 15-min incubation in 10 per cent hydroperoxide in methanol, followed by two further alcohol washes and a 1-min soak in running water. The sections were then blocked with swine serum (DakoPatts, Cambridge, UK) at a dilution of 1 : 5 for 30 min at room temperature. The excess serum was removed and a single section of each specimen was incubated for 60 min with one of the following rabbit antibodies diluted 1 : 400: antiamidated gastrin-17, antiglycine-extended gastrin-17 or antiprogastrin antiserum (at a final protein concentration of 2 µg/ml; provided by Dr A. Varro, University of Liverpool, Liverpool, UK). For all the above antisera, normal rabbit serum was used as a negative control. Gastrin receptor peptide (GRE) 1 antiserum (directed against the amino-terminal domain of the human gastrin/CCKB receptor) was used at a final protein concentration of 2 µg/ml with and without preabsorption with the GRE-1 peptide (Aphton Corporation, Woodland, California, USA)[17]. Excess primary antibody was removed by two 5-min soaks in phosphate-buffered saline (PBS; pH 7·2). The sections were then incubated with the secondary antibody at room temperature (biotinylated swine antirabbit immunoglobulin diluted 1 : 400; DakoPatts) for 60 min. Following two further washes in PBS, horseradish peroxidase-conjugated avidin antibody (DakoPatts) was applied for 30 min. Peroxidase activity was identified by applying 3,3′-diaminobenzidine tetrachloride (Sigma, Poole, UK) for 10 min at room temperature, after two PBS washes. The sections were rinsed in water, soaked in 0·5 per cent copper sulphate and counterstained with haematoxylin. Finally the sections were dehydrated in alcohol, cleared in xylene and mounted with coverslips.

Positive controls included gastric antrum for the gastrin antisera and fundus for the GRE-1 antiserum. The slides were assessed using the Leica QW500IW image analysis system and Qwin standard software (Leica Imaging Systems, Cambridge, UK). This calculates the percentage positive staining of a tissue section by expressing the area of positive staining as a percentage of the whole tissue area. Ten fields in each section were analysed and a percentage positivity of staining was obtained by calculating the median of the ten fields.

Statistical analysis

Statistical analysis of increasing protein expression of progastrin, glycine-extended gastrin, amidated gastrin and the CCKB receptor was achieved with the Jonckheere–Terpstra non-parametric test, using SPSS 9.0 for windows (SPSS®, Chicago, Illinois, USA). $P < 0·05$ was considered significant.

Results

The gastric antrum (*Fig. 1*) showed expression of all the gastrin species in the cytoplasm of the G cells. No expression of the CCKB receptor was evident, as expected. In the normal fundus (*Fig. 2*), there was no expression of the

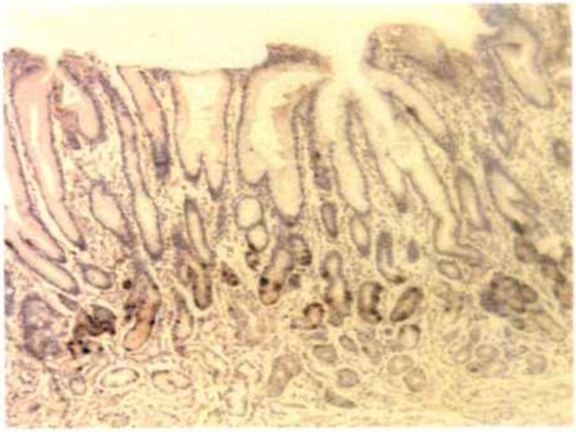

Fig. 1 Progastrin immunoreactivity in G cells of the gastric antrum (haemotoxylin-eosin counterstain, original magnification × 10)

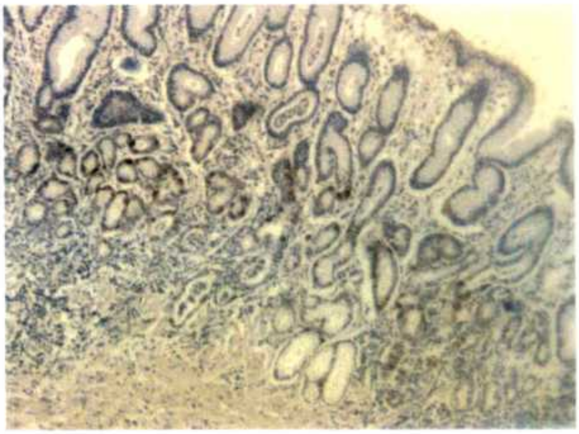

Fig. 2 Cholecystokinin B receptor immunoreactivity in parietal and entero-chromaffin-like cells of the gastric fundus (haemotoxylin-eosin counterstain, original magnification × 20)

Table 1 Gastrin and cholecystokinin B receptor expression by premalignant and malignant gastric lesions

	Median percentage positive staining			
	CCKB receptor	Progastrin	Glycine-extended gastrin	Amidated gastrin
Atrophic gastritis	4·67	5·36	3·96	4·04
Intestinal metaplasia	8·48	6·45	10·55	10·18
Mild dysplasia	10·28	4·83	11·71	14·37
Moderate dysplasia	12·13	10·78	13·17	14·66
Severe dysplasia	29·23	24·28	32·47	34·27
Gastric adenocarcinoma	33·62	33·68	34·92	38·37

Fifteen samples per condition were analysed. Percentage positive staining = area of positive staining/total tissue area × 100. CCKB, cholecystokinin B

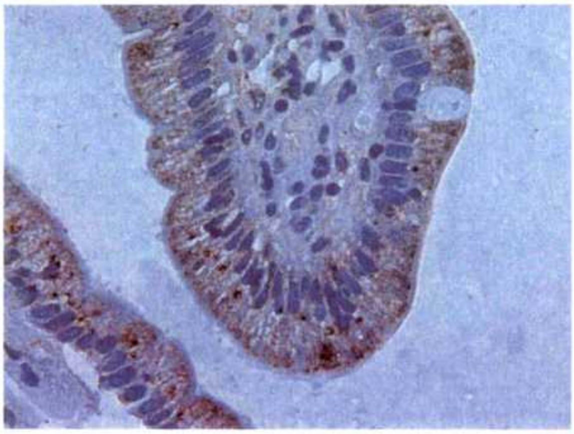

Fig. 3 Amidated gastrin immunoreactivity in a representative sample of gastric intestinal metaplasia (haemotoxylin-eosin counterstain, original magnification × 20)

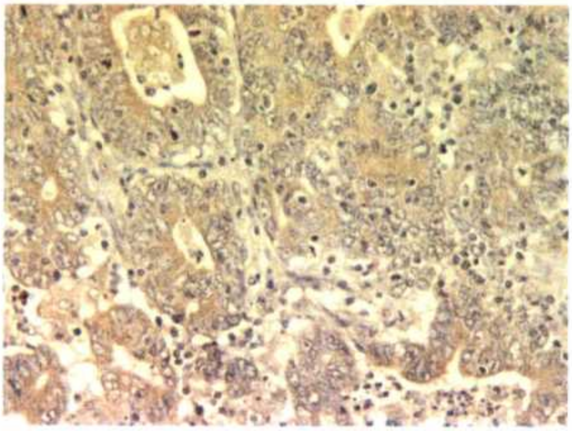

Fig. 4 Amidated gastrin immunoreactivity in a representative sample of intestinal-type gastric cancer (haemotoxylin-eosin counterstain, original magnification × 10)

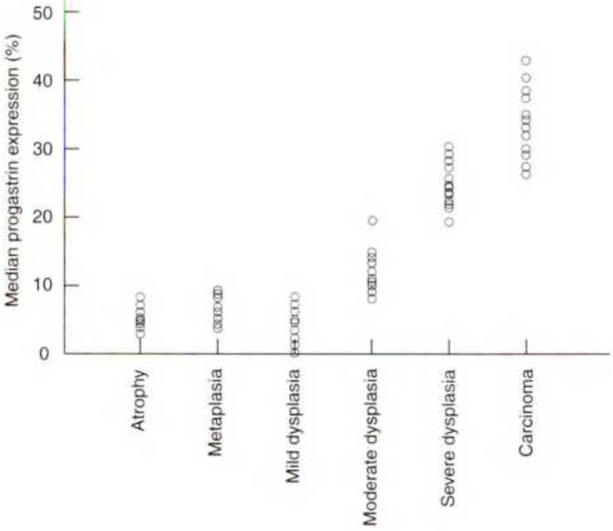

Fig. 5 Progastrin expression by gastric malignant and premalignant lesions. $z = 8{\cdot}954$, $P < 0{\cdot}0001$ (Jonckheere–Terpstra test)

gastrin species, but the CCKB receptor was observed on ECL and parietal cells as predominantly nuclear staining.

Table 1 displays the median percentage positive staining results. All 15 specimens of each lesion showed positive staining for progastrin, glycine-extended gastrin, amidated gastrin and the CCKB receptor. *Fig. 3* shows a representative field from a gastric intestinal metaplasia specimen and *Fig. 4* shows a representative intestinal-type gastric cancer, both stained for amidated gastrin. Increasing progastrin expression (median positive staining increased from 5·36 to 33·68 per cent) (*Fig. 5*) was seen along the pathway from antral gastritis to gastric adenocarcinoma ($z = 8{\cdot}954$,

$P<0\cdot0001$). The same pattern was seen for glycine-extended gastrin (median positive staining increased from 3·96 to 34·92 per cent) ($z=9\cdot734$, $P<0\cdot0001$) and for amidated gastrin (median positive staining increased from 4·04 to 38·37 per cent) ($z=10\cdot473$, $P<0\cdot0001$). Expression of the CCKB receptor (median positive staining increased from 4·67 to 33·62 per cent) followed an identical pattern and there was a highly significant ($z=10\cdot199$, $P<0\cdot0001$) increase in expression from atrophic gastritis to gastric adenocarcinoma.

Staining intensity for the CCKB receptor was greatest at the nucleus. This is a result of rapid internalization and translocation following ligand binding to the receptor[18,19].

Discussion

The association between gastrin and gastric cancer is well established. The gastrin gene has been shown to be activated in human gastric cancer cells[10], and stimulates the growth of gastric cancer cell lines *in vitro*[20–22], in primary human gastric tumour tissue[22,23] and in *in vivo* xenograft models[10,24,25]. The precursor, glycine-extended gastrin-17, also stimulates the growth of gastric carcinomas[26]. The exact role of gastrin in the development of gastric cancer has yet to be determined.

The results of the present study demonstrate that gastrin and the CCKB receptor are activated early in the progression to the intestinal type of gastric cancer. Along this cascade it can be seen that there is increased expression of different gastrin species and the CCKB receptor. Progastrin is expressed at a lower level than the other gastrin species; this indicates either constitutive secretion or that progastrin processing occurs by intact post-translational mechanisms.

Mature and precursor gastrin forms have been shown to have a proliferative action in various malignancies[12–15]. This proliferative action can be mediated via autocrine or paracrine pathways[27,28]. For these pathways to exist a cell must expel both the growth factor and an appropriate receptor. These results demonstrate that the components of the gastrin autocrine pathway are present and may be acting in premalignant gastric lesions. Increased expression of gastrin and the CCKB receptor is seen in tissue with greater malignant potential, perhaps implying that the autocrine pathway becomes more important.

Gastrin can not only directly influence the growth of the gastric epithelium but it has also been shown to increase the expression of other members of the epidermal growth factor family implicated in gastric carcinogenesis. It has been shown to stimulate the production of transforming growth factor α, amphiregulin, heparin-binding epidermal growth factor and regenerating protein, and can be coamplified with c-*erbB2*[29,30–33]. Thus once the gastrin gene is activated in premalignant gastric epithelium it can interact with numerous other growth factors, possibly leading to the progression to malignancy.

What activates the gastrin gene in gastric premalignant lesions is unclear. However, it has been shown that K-*ras* induces gastrin gene expression in colon cancer cells[34]. It is possible therefore that once an area of atrophic epithelium acquires a K-*ras* mutation, the gastrin gene will be activated.

Atrophic gastritis, intestinal metaplasia and epithelial dysplasia are accepted precursors of the intestinal type of gastric adenocarcinoma. However, the detection of these lesions in patients at gastroscopy is operator dependent and the full clinical significance of these lesions in areas of low incidence such as the UK remains to be identified. With increased understanding of the factors involved in the progression to malignancy, identification of lesions that require more close surveillance or excision may become possible.

Acknowledgements

This research was funded by a grant from the Aphton Corporation, Woodland, California, USA.

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Original article

Analysis and surgical treatment of persistent dysphagia after Nissen fundoplication

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Background: After Nissen fundoplication, troublesome dysphagia develops in 5–10 per cent of patients. The mechanism of dysphagia has not been fully resolved, in spite of a number of studies focusing on oesophageal motility and lower oesophageal sphincter (LOS) dynamics. Tightness and length of the wrap have had considerable attention, without giving a fully satisfactory explanation of the pathophysiological mechanism.

Methods: Eighteen patients with persistent dysphagia after Nissen fundoplication needing reoperation were studied. Eighteen patients, matched for age and sex, without dysphagia after Nissen fundoplication were used as controls. Reoperation consisted of conversion of a 360° into a 270° wrap. Barium swallow, endoscopy, oesophageal manometry and 24-h pH monitoring were performed before and after (re)operation.

Results: Peristaltic amplitude, velocity and duration of contraction were not significantly influenced by operation. In 16 of 18 patients with dysphagia, LOS relaxation was incomplete and the residual relaxation pressure was significantly higher than that in the group without dysphagia ($P < 0{\cdot}01$). No correlation was found between LOS pressure and peristaltic amplitude, nor between LOS pressure and ramp pressure in the distal oesophagus. After reoperation, basal LOS pressure decreased significantly ($P < 0{\cdot}01$) and LOS relaxation was complete in all but three patients; residual relaxation pressure decreased ($P < 0{\cdot}01$) and was significantly lower than that after uncomplicated Nissen fundoplication. In the latter group, LOS pressure, residual relaxation pressure and ramp pressure increased significantly after operation ($P < 0{\cdot}01$).

Conclusion: A return to complete LOS relaxation and a decrease in residual relaxation pressure play an important role in resolving dysphagia.

Paper accepted 14 November 2000

British Journal of Surgery 2001, 88, 569–576

Introduction

Antireflux surgery has proved to be an effective treatment for gastro-oesophageal reflux disease (GORD). Studies with follow-up of more than 10 years have shown that long-term success rates of 80–90 per cent can be obtained[1–4]. However, in 10–20 per cent of patients reflux-related symptoms persist or new symptoms, such as persistent dysphagia, inability to belch or vomit, fullness and bloating, appear[5,6]. Persistent dysphagia occurs in 0–17 per cent of patients after open Nissen fundoplication; the incidence after laparoscopic surgery seems to be even higher and ranges from 7 to 30 per cent[7,8]. The mechanism of dysphagia following antireflux surgery still remains unclear which makes it impossible to predict which patients are at risk[9–12]. Research has focused on the length and tightness of the fundoplication[13–15], and on function of the oesophageal body[16–21]. Less attention has been paid to the more subtle dynamics of the lower oesophageal sphincter (LOS) in patients with dysphagia after Nissen fundoplication and the interaction with oesophageal body motor function.

In this report a group of patients with severe dysphagia after Nissen fundoplication needing reoperation is described. The effect of reoperation by the Belsey Mark IV procedure on symptoms, LOS and oesophageal motility, which might provide an explanation for the mechanism of dysphagia, is presented. A group of patients, matched for age and sex, without dysphagia after Nissen fundoplication has been studied for comparison.

Patients and methods

Between 1982 and 1997, 18 patients were reoperated because of persistent dysphagia after Nissen fundoplication. Dysphagia was considered persistent if it lasted for more than 3 months, resulted in weight loss of more than 5 kg and did not respond to dilatation of the oesophagogastric junction.

All patients were reoperated by means of the Belsey Mark IV procedure: a 270° fundoplication with creation of a posterior buttress of the right crus through a left-sided thoracotomy in the sixth intercostal space[22,23]. The same surgical team performed all procedures. Most patients had a preoperative and postoperative barium swallow to image the position of the fundoplication. All patients had endoscopy, oesophageal manometry and 24-h pH monitoring, before and 3 months after the Belsey Mark IV procedure.

The manometric characteristics before and after reoperation were compared with those of a group of 18 patients (matched for age and sex) without dysphagia after Nissen fundoplication. These patients were operated betweeen 1994 and 1997, by the same team; all had a floppy 3·0–3·5-cm Nissen fundoplication with division of the short gastric vessels after complete preoperative evaluation consisting of standardized clinical history, upper gastrointestinal endoscopy, manometry and 24-h pH monitoring.

Symptoms

In both groups, the preoperative and postoperative symptoms were scored according to a system combining frequency (daily, once a week, once a month, or less) and severity (severe, moderate, mild, no symptoms)[24] for heartburn, regurgitation and dysphagia. Dysphagia was defined as an uncomfortable sensation of food sticking in the oesophagus shortly after or while eating solid food and liquids. Reoperation was considered successful when dysphagia was abolished without the induction of recurrent GORD. Nissen fundoplication was called 'uncomplicated' when all symptoms of GORD had been treated successfully and no dysphagia had developed. This group will henceforth be referred to as the 'uncomplicated Nissen' group.

Radiological examination of the oesophagus

Barium oesophagogastrography was performed before and after (re)operation to obtain information about oesophageal emptying but mainly to identify the position of the wrap.

Upper gastrointestinal endoscopy

Endoscopic findings were graded according to the criteria of Savary and Miller[25]: grade 0, normal mucosa, with no lesions; grade I, single or non-confluent multiple mucosal erosions; grade II, confluent erosions, not including the whole circumference of the oesophagus; grade III, confluent erosions including the whole oesophagus, but without stenosis; and grade IV, chronic lesions, ulcers and/or stenosis. The presence of Barrett's epithelium was indicated separately. The endoscopist's impression of the tightness of the wrap was also recorded.

Oesophageal manometry

All medication that could affect oesophageal motility was stopped at least 48 h in advance. Manometry was performed after an overnight fast, using a water-perfused catheter with a sleeve sensor (Dent Sleeve, Adelaide, Australia) connected to a pneumohydraulic perfusion pump (Arndorfer Medical Specialities, Greendale, Wisconsin, USA). The catheter was passed transnasally into the stomach and the sleeve sensor was positioned at the central point of the LOS.

Intraluminal oesophageal pressures were recorded at 5, 10 and 15 cm above the upper margin of the LOS. The manometric response to ten standardized wet swallows (10-ml water bolus) was recorded. Peristaltic wave amplitude and duration of contraction were calculated for the proximal (15 cm above the LOS), mid (10 cm) and distal (5 cm) part of the oesophagus. The velocity of peristalsis for the proximal and distal part of the oesophagus was calculated from peak-to-peak intervals between peristaltic waves between adjacent transducers. The ramp pressure, defined as the intraoesophageal pressure increase just before the peristaltic wave[26,27], was determined for the distal part of the oesophagus.

The mean end-expiratory LOS pressure was determined over a period of 10 min. The end-expiratory gastric baseline pressure served as the zero reference point. The residual pressure of the LOS during relaxations, in response to wet swallows, was measured as well as the mean percentage of LOS relaxations. LOS relaxation was defined as normal if it exceeded 90 per cent with a residual pressure below 8 mmHg[28]. Correlations between basal LOS pressure, amplitude and velocity in the distal part of the oesophagus and ramp pressure were assessed before and after (re)operation for patients with and without dysphagia after Nissen fundoplication.

Continuous pH monitoring

All studies were performed as outpatient procedures after an overnight fast. All medication that could possibly interfere with the results was stopped at least 48 h before pHmetry in the 1980s and 5 days before testing in the 1990s. Since GORD was not present in the vast majority of these patients, this change in approach can only have been of minor influence. The intraoesophageal pH was measured for 24 h using a pH glass electrode (model LOT440; Ingold, Urdorf, Switzerland). The catheter was introduced through the nose into the oesophagus and positioned 5 cm above the manometrically determined upper margin of the LOS. The pH signal was recorded in a digital data logger, using a sampling rate of 0·2 Hz. Reflux variables were calculated for the 24-h data using a commercially available analysis program. Reflux variables used in this study were percentage of time with pH less than 4 (total, upright, supine), number of reflux episodes (total, upright, supine) and mean duration of reflux episodes (total, upright, supine). Data from 24-h pH monitoring of 27 asymptomatic volunteers served as control values; pathological reflux was defined as the total proportion of time at pH below 4 of 4·4 per cent or more, upright 4·4 per cent or more and supine 1·2 per cent or more[29].

Statistical analysis

Results are expressed as median (range). The paired samples *t* test was used for statistical comparison of manometric variables obtained before and after (re)operation. The Mann–Whitney *U* test and non-parametric correlation coefficient (Spearman's rank test) were used for comparisons between the two groups. The relation between LOS pressure, amplitude and velocity of the contractions in the distal oesophagus and ramp pressure was calculated using Spearman's rank correlation test. All tests were performed using the statistical software package SPSS 7.5.2 for Windows (SPSS, Chicago, Illinois, USA). The significance level was set at $P < 0·05$.

Results

Eighteen patients were reoperated for persistent dysphagia after Nissen fundoplication. The group consisted of seven men and 11 women with a median age of 50 (range 25–61) years, with a median follow-up of 3 (range 1–16) years. Most patients had undergone one or more dilatations without permanent success. The control group consisted of seven men and 11 women with a median age of 44 (range 27–61) years and follow-up ranged from 1 to 8 (median 2) years. All these patients had the full-scale preoperative and postoperative evaluation.

Radiological examination in patients with dysphagia invariably showed some degree of delayed oesophageal emptying, with some dilatation of the distal oesophagus. In one patient the fundoplication had slipped around the stomach (telescoping) and two patients had a paraoesophageal hernia. No clear explanation for dysphagia could be found in the remaining patients. In all cases the endoscope could be introduced into the stomach without appreciable resistance.

Surgical complications

One patient in the dysphagia group developed a wound abscess and one patient in the control group had a postoperative pneumothorax. Recurrent GORD was diagnosed in three patients after reoperation. These patients were treated medically. Another patient in this group needed a partial gastrectomy because of intractable delayed gastric emptying, probably due to vagal nerve damage. There was no surgical death.

Effect of operation on symptoms

After reoperation all patients experienced improvement of dysphagia. In ten of the 18 patients dysphagia was completely resolved and eight patients had mild residual symptoms with a frequency of about once a month. Reoperation reduced the mean (range) composite score for dysphagia from 3 (2–3) to 0 (0–2) ($P < 0·001$). The scores for regurgitation and heartburn were not significantly affected. After reoperation, the scores for dysphagia were no longer different from those of the control group ($P = 0·75$). In the uncomplicated Nissen group there was no significant dysphagia and reflux symptoms were resolved.

Effect of operation on oesophageal body motility

Effect of reoperation

The effect of reoperation on oesophageal motor function is presented in *Table 1*. The percentage of primary peristaltic contractions, amplitude of contractions, contraction velocity and duration, and ramp pressure were not significantly affected by conversion from 360° to 270° fundoplication. The ramp pressure in patients with dysphagia before reoperation was no different from that in patients after uncomplicated Nissen fundoplication (*Fig. 1*).

Effect of uncomplicated Nissen fundoplication

Again, the percentage of primary peristaltic contractions, amplitude of contractions, and contraction velocity were not significantly altered by the operation. Duration of distal contractions and ramp pressure both increased (from a median of 2·9 (1·9–4·3) to 3·4 (2·0–4·7) s ($P = 0·05$) and from

Table 1 Results of oesophageal manometry in 18 patients with persistent dysphagia after Nissen fundoplication before and after reoperation (Belsey Mark IV), and in 18 patients before and after Nissen fundoplication not leading to dysphagia

	Dysphagia after Nissen			Uncomplicated Nissen		
	Before Belsey Mark IV	After Belsey Mark IV	P^*	Before Nissen	After Nissen	P^*
Oesophageal body						
Primary peristalsis (%)	100 (20–100)	90 (30–100)	0·58	100 (80–100)	90 (60–100)	0·05
Ramp pressure (mmHg)	10·3 (0·0–27·0)	10·0 (0·0–17·3)	0·95	10·1 (0·8–21·5)	14·3 (0·8–25·1)	< 0·01
Lower oesophageal sphincter						
End-expiratory pressure (mmHg)	20·8 (5·3–38·0)	11·1 (0·8–32·3)	< 0·01	4·5 (1·5–15·0)	9·0 (4·5–16·5)	< 0·01
Relaxation (%)	65 (0–100)	100 (80–100)	< 0·01	100 (80–100)	100 (75–100)	0·14
Residual relaxation pressure (mmHg)	6·9 (0·2–17·0)	0·4 (0–4·1)	< 0·01	0·5 (0–3·9)	2·4 (0–7·7)	< 0·01

Values are median (range). *Paired samples t test

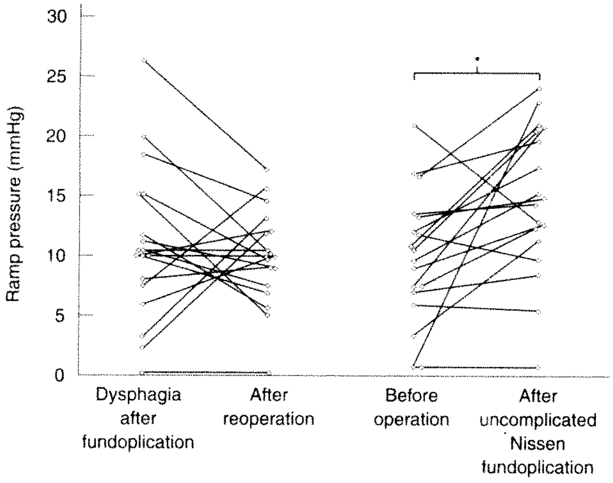

Fig. 1 Ramp pressure in 18 patients with dysphagia after Nissen fundoplication before and after reoperation, and in 18 patients before and after uncomplicated Nissen fundoplication. $^*P<0\cdot01$ (paired samples t test)

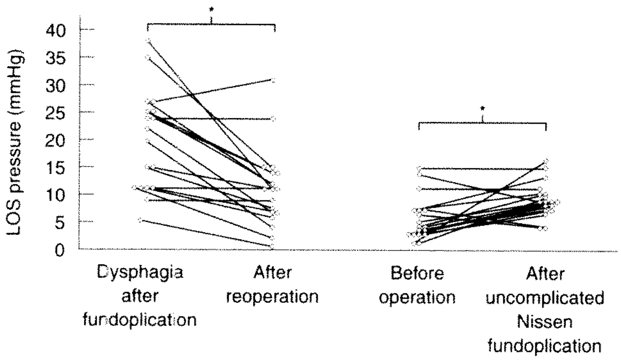

Fig. 2 End-expiratory lower oesophageal sphincter (LOS) pressure in 18 patients with dysphagia after Nissen fundoplication before and after reoperation, and in 18 patients before and after uncomplicated Nissen fundoplication. $^*P<0\cdot01$ (paired samples t test)

10·1 (0·8–21·5) to 14·3 (0·8–25·1) mmHg ($P<0\cdot01$) respectively).

Effect of operation on lower oesophageal sphincter dynamics

Effect of reoperation

Preoperatively the residual relaxation pressure in patients with dysphagia was significantly higher than in the group without dysphagia ($P<0\cdot01$). End-expiratory LOS pressure and residual relaxation pressure both decreased significantly after reoperation (both $P<0\cdot01$) and were no longer different from values obtained in patients after uncomplicated Nissen fundoplication (*Figs 2* and *3*). The percentage of swallow-induced sphincter relaxations returned to normal (*Fig. 4*).

Before reoperation a negative correlation was found between the percentage of complete swallow-induced relaxations and the ramp pressure ($r=-0\cdot49$; $P=0\cdot04$). No significant correlation was observed between end-expiratory LOS pressure and distal peristaltic amplitude ($r=0\cdot40$; $P=0\cdot10$), peristaltic velocity ($r=0\cdot30$; $P=0\cdot23$) or ramp pressure ($r=0\cdot25$; $P=0\cdot31$). Residual relaxation pressure and ramp pressure also showed no significant correlation ($r=0\cdot24$; $P=034$). After reoperation a significant correlation was found between the end-respiratory LOS pressure and distal peristaltic amplitude (r = 0·49; P = 0·04). The length of the high-pressure zone at the oesophagocardiac junction was not affected by reoperation and fell in the same range as values obtained before and after uncomplicated Nissen fundoplication.

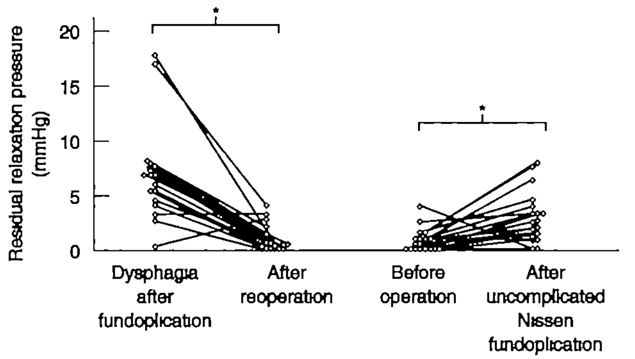

Fig. 3 Residual relaxation pressure in 18 patients with dysphagia after Nissen fundoplication before and after reoperation, and in 18 patients before and after uncomplicated Nissen fundoplication. $^*P<0\cdot01$ (paired samples *t* test)

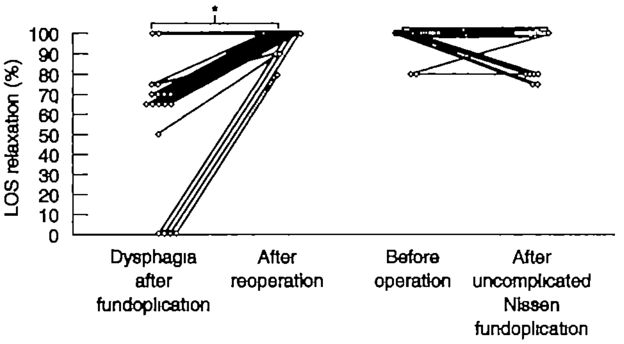

Fig. 4 Relaxation of the lower oesophageal sphincter (LOS) in 18 patients with dysphagia after Nissen fundoplication before and after reoperation, and in 18 patients before and after uncomplicated Nissen fundoplication. $^*P<0\cdot01$ (paired samples *t* test)

Effect of uncomplicated Nissen fundoplication

End-expiratory LOS pressure and residual relaxation pressure were significantly increased by 360° fundoplication (both $P<0\cdot01$). End-expiratory LOS pressure after Nissen fundoplication fell in the same range as that after reoperation, whereas residual relaxation pressure was higher than that after reoperation ($P<0\cdot01$). The length of the LOS/high-pressure zone was no different from that before and after reoperation. A significant correlation between end-expiratory LOS pressure and distal peristaltic velocity ($r=0\cdot63$; $P<0\cdot01$) was present in patients with GORD, but not after Nissen fundoplication. After Nissen fundoplication a significant correlation was found between LOS pressure and the distal peristaltic amplitude ($r=0\cdot58$; $P=0\cdot013$). The ramp pressure showed a significant increase after operation ($P<0\cdot01$) (*Fig. 1*).

Effect of reoperation on endoscopic findings

Before reoperation two patients had grade I and one had grade II oesophagitis. After reoperation oesophagitis was cured in these patients but grade I oesophagitis was seen in one other patient. There were no significant differences between the groups in grades of oesophagitis before and after (re)operation.

Effect of operation on 24-h pH profile

The median total reflux time in patients with dysphagia after Nissen fundoplication was similar before and after reoperation (0·8 (0–16·5) *versus* 1·8 (0–14·9) per cent; $P=0\cdot95$); after reoperation 14 patients fell within the normal range, three were borderline abnormal and one had pathological acid exposure (14·9 per cent of total time).

A significant reduction in total reflux time from 11·2 (0·3–21·7) to 0·9 (0–12·0) per cent was measured in patients without dysphagia after Nissen fundoplication ($P<0\cdot01$); after operation, 15 patients had normal acid exposure, two were borderline abnormal and in one acid exposure was excessive (12·0 per cent of total time).

Acid reduction after Nissen fundoplication was no different from that after the Belsey Mark IV redo procedure ($P=1\cdot0$).

Discussion

Dysphagia is a persistent problem after Nissen fundoplication and the mechanism is incompletely understood. The length of the fundic wrap has been mentioned as the potential basis for dysphagia. In the 1970s and 1980s DeMeester *et al.*[30] proposed that length of the fundoplication and basal LOS pressure were the two major factors controlling dysphagia. In the past few years, no severe dysphagia has been observed after open Nissen fundoplication with a wrap of 3·0–3·5 cm, whereas a dysphagia rate of 12 per cent has been reported after the laparoscopic procedure, in the same period with essentially the same procedure[31]. In the present study, in both groups, the length of the high-pressure zone on manometry was also about 3·5–4·0 cm. Therefore, length as such does not seem to be a very important determinant of dysphagia.

Different aspects of oesophageal body motor function and the dynamics of the LOS, as variables reflecting the tightness of the wrap, have also been examined in detail. As expected, no differences in primary peristaltic contractions were observed, although in both groups some patients met the criteria of a non-specific motility disorder. However, these were not over-represented in the dysphagia group. A relation between LOS pressure and distal peristaltic amplitude and a decrease in peristaltic amplitude after relief of dysphagia was anticipated. Although such a decrease was not observed in any of the three oesophageal segments, median values tended to be higher before reoperation and there was a possible correlation between LOS pressure and distal amplitude after reoperation and uncomplicated Nissen. These findings suggest that distal amplitude adapts to the barrier at the lower end of the oesophagus and that insufficient adaptation to a high LOS pressure plays a role in dysphagia. Duration of contraction and peristaltic velocity were not affected by reoperation.

The so-called ramp pressure represents the intrabolus pressure in front of the actual contraction. An increased ramp pressure was not a co-phenomenon of dysphagia in this study, although this was suggested by Mittal *et al.*[26]. Mathew *et al.*[27] found an increase in ramp pressure after laparoscopic Nissen fundoplication but without correlation with symptoms of dysphagia. In fact, in this study it seems that an increase in ramp pressure 'protects' against dysphagia after Nissen fundoplication, because an increased ramp pressure was not observed in patients with dysphagia after a Nissen procedure and conversion to a partial fundoplication did not lead to a demonstrable decrease in ramp pressure. Intrabolus pressure in the distal oesophagus is likely to be determined by a multitude of factors: amplitude and velocity of oesophageal peristalsis, oesophageal diameter and resistance at the oesophagogastric junction. Many of these factors may be altered in dysphagia after fundoplication.

Basal LOS pressure was highest in the dysphagia group, but there was a large overlap with patients after reoperation and after uncomplicated fundoplication. After reoperation the basal LOS pressure was in the same range as that after uncomplicated Nissen fundoplication. Basal LOS pressure does not discriminate between dysphagia and non-dysphagia after surgery. Incompleteness of relaxation was a more consistent finding in the dysphagia group. This phenomenon was observed in the majority of patients with dysphagia as the reason for reoperation. Relief of dysphagia was accompanied with return of complete relaxation in almost all patients. Complete relaxation after swallowing does not seem to be an absolute prerequisite for absence of dysphagia, because incomplete relaxation is commonly found after uncomplicated Nissen fundoplication.

Residual relaxation pressure was highest in patients with dysphagia and it became identical to that seen in patients with GORD after conversion to partial fundoplication. The combination of incomplete sphincter relaxation with raised residual relaxation pressure was almost invariably present in patients with dysphagia. The present data on residual relaxation pressure are in concordance with recent observations by the Adelaide group, who found no effect of Nissen fundoplication on basal LOS pressure, but a significant increase in residual relaxation pressure in patients without dysphagia[32]. In another study they showed an increase in basal LOS pressure after Nissen fundoplication in combination with an increase in residual relaxation pressure[33]. After partial fundoplication, the residual relaxation pressure was higher than that before surgery but lower than that after Nissen fundoplication.

The question remains as to how dysphagia after antireflux surgery may be prevented. Several authors have shown that the incidence of dysphagia is lower after partial fundoplication than after a 360° wrap. Hunter *et al.*[34] compared, in a non-randomized study, the Nissen, Nissen–Rosetti and Toupet procedures and showed that the incidence of dysphagia was highest after Nissen–Rosetti and lowest after the Toupet procedure. They also drew attention to the aspect of the wrap on postoperative endoscopy and showed that torsion in the wrap, leading to a 'spiral' appearance of the fundoplication, might be important in causing dysphagia. Lundell *et al.*[35], who compared the Nissen and Toupet procedures in a randomized study, reported similar results. However after more than 1 year the difference between the two techniques had faded. The risk of dysphagia is very low after the Belsey Mark IV procedure[36], but also after open Nissen fundoplication with a wrap of 3–4 cm in length[31]. Prevention is difficult when the results are so confusing. Defective oesophageal body motor function has also been held responsible for the development of dysphagia[37–39]. In a study by Baigrie *et al.*[40] of patients who had undergone a 360° fundoplication irrespective of their preoperative oesophageal peristalsis, no difference in subjective and objective outcome was found in patients with disturbed oesophageal motility. Three of the present patients with dysphagia had motility disorders that improved after reoperation.

Prospective criteria to predict dysphagia could not be identified from the patients studied. Despite extensive research dysphagia after antireflux surgery remains difficult to manage. No preoperative criteria are currently available to predict dysphagia after fundoplication. Kamolz *et al.*[41] have shown that patients with low expectations of their own abilities are more likely to develop dysphagia after antireflux surgery and they plea for adopting prognostic psychological tests before antireflux surgery to select the proper patients.

Once dysphagia has developed, an unequivocal pathophysiological reason for the impaired passage of food through the high-pressure zone cannot usually be identified. Barium swallow may show a slight dilatation of the oesophagus with delayed oesophageal emptying but usually without an explanation even for severe dysphagia. The endoscope passes easily through the oesophagus into the stomach and the endoscopist tends to challenge the diagnosis of obstructive disease. Basal LOS pressure may be in the normal range and incomplete relaxation is often but not always reported. When dietary advice is not sufficient, dilatation is attempted to relieve symptoms and to prevent weight loss. Wo *et al.*[42] noted that dilatation was successful if dysphagia was persistent after the first operation. Dilatation was far less successful after a second or third operation. The group of patients studied was not homogeneous, because contrast radiography showed a 'slipped Nissen' in about one-third of the patients studied. This is in contrast to the present study in which one of 18 patients had a slipped Nissen fundoplication and one a paraoesophageal hernia with the fundoplication *in situ*. If dilatation fails, conversion from a 360° wrap into a partial fundoplication is the only effective way to solve the problem. A successful outcome finally proves that the patient's symptoms were indeed caused by functional obstruction at the level of the LOS.

In conclusion, incomplete relaxation of the LOS with an increase in residual relaxation pressure is a consistent finding in dysphagia. However, these phenomena do not allow complete separation of patients with dysphagia from those without.

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Original article

Laparoscopic antireflux surgery in the treatment of the acid-sensitive oesophagus

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Background: Approximately 10 per cent of patients referred for 24-h oesophageal pH tests with symptoms suggestive of gastro-oesophageal reflux disease will have a normal endoscopic examination and normal distal oesophageal acid exposure times, but a clear temporal correlation between their symptoms and episodes of acid reflux. These patients have an 'acid-sensitive oesophagus', which forms part of the spectrum of reflux-related conditions. Their response to antireflux surgery has not been reported previously. This study represents a prospective cohort analysis of a clearly defined group of patients with acid-sensitive oesophagus who have undergone laparoscopic antireflux surgery.
Methods: Nineteen patients (nine male and ten female; median age 32 years) underwent laparoscopic antireflux surgery for acid-sensitive oesophagus. All had had an incomplete response to medical therapy.
Results: Eighteen of 19 patients were graded Visick I or II at 6 months after operation; all 16 patients followed for 1 year were graded Visick I or II. There were significant falls in DeMeester symptom score (4·0 *versus* 0·5; $P < 0.001$), symptom events (20 *versus* none; $P < 0.001$), number of reflux episodes (17 *versus* two; $P < 0.001$) and overall acid exposure times (1·2 *versus* 0·3 per cent; $P < 0.001$) after operation.
Conclusion: Laparoscopic antireflux surgery is a valid and effective treatment for patients with an acid-sensitive oesophagus.

Presented in poster form to the British Society of Gastroenterology, Birmingham, March 2000 and the American Gastroenterological Association, San Diego, May 2000
Paper accepted 5 December 2000
British Journal of Surgery 2001, **88**, 577–582

Introduction

Laparoscopic antireflux surgery is a well established procedure of proven benefit for patients with symptomatic gastro-oesophageal reflux disease (GORD)[1–3]. However, not all patients with reflux-related symptoms fulfil the traditional endoscopic or acid exposure criteria for a diagnosis of GORD. Approximately 10 per cent of patients referred for 24-h oesophageal pH tests with symptoms suggestive of GORD will have both a normal endoscopic examination and normal distal oesophageal acid exposure time (AET), but a clear temporal relation between their symptoms and episodes of acid reflux. These patients can be said to have an 'acid-sensitive oesophagus' (ASO), which forms part of the spectrum of reflux-related conditions[4,5]. Some will respond fully to medical acid suppression[6] but, as with true pathological GORD, a proportion will remain symptomatic despite appropriate medical therapy, or will be unable to take medical therapy owing to intolerable side-effects. The aim of this study was to assess the results of laparoscopic antireflux surgery in this group.

Patients and methods

Between 1993 and 1999, 167 laparoscopic antireflux procedures were performed by a single surgeon in a district general hospital. Of these, 19 patients had a diagnosis of ASO. The definition of ASO was made on the basis of symptoms, findings at endoscopy and the results of 24-h distal oesophageal pH-metry. All patients had symptoms of gastro-oesophageal reflux, normal endoscopy (i.e. absence of both endoscopic oesophagitis and hiatus hernia), and two separate 24-h pH tests with a normal AET, but with a positive symptom index. All patients corresponded to the classification $A_0F_0P_0$, where A_0 indicates normal hiatal anatomy at endoscopy, F_0 indicates a total AET of less than 4 per cent, and P_0 indicates the absence of endoscopic oesophagitis[7].

All data were collected prospectively. Thirteen patients had two separate and normal preoperative 24-h pH tests preceded by stationary oesophageal manometry. Six patients had two separate and normal preoperative pH tests performed by the 'pull-back' technique[8] but without preceding manometry (see below). There were no significant differences between these two groups in terms of patient characteristics, physiological tests or subjective assessments so they are presented here as a single group.

Before initial oesophageal function tests, patient symptom information was obtained using a standardized symptom questionnaire, which included a DeMeester symptom score[9], details of symptom duration and any medication taken for reflux symptoms. All patients described heartburn and regurgitation; heartburn predominated in four, regurgitation predominated in six and both symptoms were equally dominant in nine. All patients underwent surgery because of failure of medical therapy to control their symptoms fully. Ten patients had symptoms despite at least double maintenance doses of proton pump inhibitors (PPIs), i.e. omeprazole 40 mg daily or lansoprazole 60 mg daily. Four patients had maintenance doses of PPIs but were unable to tolerate higher doses owing to side-effects. One patient was unable to take even maintenance doses of PPIs because of depression, and was treated with ranitidine 150 mg three times daily. Two adolescents (aged 12 and 15 years) had reduced doses of PPIs according to dosage recommendations at the time, and one (aged 14 years) was treated with Gaviscon® (Reckitt and Colman, Hull, UK) before PPIs were licensed for use in adolescents. Similarly one adult was treated with ranitidine before PPIs were licensed for maintenance treatment in GORD. Median duration of symptoms before surgery was 36 (range 9–360) months.

All patients underwent outpatient upper gastrointestinal endoscopy. Oesophagitis, or its absence, was scored using the classification of Savary and Miller[10]. Hiatal anatomy was recorded.

Stationary manometry traces were analysed according to Castell's criteria[11]. In the 13 patients who had preoperative manometry, median lower oesophageal pressure was 12·5 (range 5–20) mmHg and lower oesophageal length was 4 (2–5) cm. Two of 13 patients had ineffective oesophageal body motility, and the remaining 11 had normal motility.

Twenty-four-hour ambulatory oesophageal pH monitoring was performed before operation in all patients. Antisecretory and prokinetic agents were omitted for 7 days before the tests. All pH studies were performed as outpatient procedures following a 6-h fast. Studies were performed using a single-use antimony pH catheter with an internal reference electrode (Zinetics 24; Medtronic, Salt Lake City, Utah, USA) and a portable digital data recorder (Flexilog™; Oakfield, Oxford, UK) which recorded and stored oesophageal pH data every 6 s. After calibration at pH 4 and pH 7, the catheter was passed transnasally into the stomach, as determined by a fall in pH to below 2·5. It was then withdrawn to lie 5 cm above the manometrically determined proximal border of the lower oesophageal sphincter. Before the introduction of oesophageal manometry, the pull-back technique was used to determine the proximal border of the lower oesophageal sphincter[8]. Here the pH catheter was withdrawn to lie 5 cm above the point at which there was a marked, persistent step up in the pH level.

No restrictions were placed upon patients' diet, fluid intake or activities. A diary was kept of the time spent supine and upright, of all symptoms experienced, and of food and liquid intake during the test period. An event marker was used by the patient to record the timing of any symptoms. The pH catheter was removed after 24 h and recalibrated to check for significant drift. Variation by more than 0·5 pH units from the pretest calibration led to the test being disregarded. Repeated preoperative pH tests were separated by an interval of at least 2 weeks. The pH data were analysed using a commercial software program (Flexisoft™ 2; Oakfield). The results of all tests were reviewed weekly by a consultant surgeon and two clinical nurse specialists. The following normal values of pH parameters were employed: percentage time upright with oesophageal pH below 4 of less than 6 per cent; percentage time supine with oesophageal pH below 4 of less than 2 per cent; total percentage time with oesophageal pH below 4 of less than 4 per cent; and Johnson and DeMeester composite score[12] of less than 16·7.

A test was deemed to be diagnostic of GORD if any one of these values was exceeded. Such a result excluded a diagnosis of ASO. A test was not deemed to be indicative of GORD if the symptom index alone was positive. A modified symptom index score was used, similar to that employed by Weusten *et al.*[13]. A reflux episode was recognized if there was a fall in pH of greater than 1·5 units from baseline lasting more than 6 s, regardless of whether the pH fell below 4. There was deemed to be an association between a patient event and a reflux episode if the event marker was pressed during the reflux episode or up to 2 min after its cessation. These events were identified by manual analysis of all traces. The symptom index was deemed positive if a minimum of 50 per cent of patient events corresponded to a reflux episode[14].

Laparoscopic floppy Nissen fundoplication was performed by fashioning a floppy 360° posterior wrap over a 56-Fr oesophageal bougie, with routine division of the short gastric vessels. A 2-cm wrap was created with three non-absorbable sutures, the proximal two of which included the anterior oesophageal wall. The completed wrap was anchored to the right pillar of the crus with a further non-absorbable suture.

Laparoscopic partial fundoplication was performed by fashioning a posterior 270° wrap, again with routine division of the short gastric vessels. Each limb of the wrap was sutured to the oesophagus using three non-absorbable sutures and to the respective pillar of the crus with a further suture.

Early on in the series no crural repair was performed as, by definition, this group of patients had no crural defect. This policy was altered to one of routinely placing a posterior crural non-absorbable suture following two late complications of mediastinal wrap herniation (see below).

Three patients underwent a laparoscopic partial fundoplication as part of a concurrent randomized surgical trial of fundoplication. All other patients underwent laparoscopic Nissen fundoplication with one conversion to an open operation on account of haemorrhage from a short gastric vessel.

Postoperative follow-up was performed by patient-completed questionnaire, DeMeester symptom score and the modified Visick score[15] (*Table 1*) at 6 weeks, 6 months and 1 year after operation. Twenty-four-hour pH tests were performed 6 months after operation.

Statistical analysis

Results are expressed as median (interquartile range), unless stated otherwise. A Mann–Whitney rank sum test was used for comparison of differences between medians in two groups, and of differences between preoperative and postoperative values within groups. Statistical significance was assumed at $P < 0{\cdot}05$.

Results

Patient details are given in *Table 2*. The median DeMeester symptom score fell from 4·0 (3·2–6·0) before operation to 0·5 (0–2·0) after operation ($P < 0{\cdot}001$) (*Fig. 1*). The number of symptom events on 24-h pH-metry fell from 20 (9–28) to 0 (0–0) ($P < 0{\cdot}001$) (*Fig. 2*). The median symptom index was 82 (59–100) per cent before operation. After operation only three patients experienced any symptoms (symptom indices 5, 25 and 50 per cent). The remaining patients had no symptoms during the postoperative 24-h pH test so no symptom index could be calculated. Total acid exposure fell from 1·2 (0·8–2·4) per cent before surgery to 0·3 (0–0·8) per cent after operation ($P < 0{\cdot}001$). The number of reflux episodes per test fell from 17 (12–28) to 2 (0–7) after operation ($P < 0{\cdot}001$). Nocturnal symptoms were rare before and after operation (both median zero). Nocturnal reflux episodes were similarly rare (median 1 (0–2) before operation *versus* 0 (0–0) after surgery; $P < 0{\cdot}05$).

Table 1 Visick grades

I	Asymptomatic
II	Minor symptoms or side-effects not interfering with life or requiring medication
III	Residual symptoms or side-effects interfering with lifestyle or requiring continuous or frequent medication
IV	Complete failure to improve symptoms/intractable side-effects

Table 2 Details of 19 patients with acid-sensitive oesophagus

Age (years)	32 (12–56)
Sex ratio (M : F)	9 : 10
Weight (kg)	70 (42–93)
Preoperative DeMeester score	4 (2–9)
Preoperative total acid exposure time (%)	1·2 (0·5–3·6)
Preoperative symptom index (%)	82 (50–100)
Operating time (min)	98 (53–150)
Postoperative hospital stay (days)	2 (1–4)
Return to work (days)	21 (7–49)

Values are median (range)

Overall, 18 of 19 patients were graded Visick I or II at 6 months, and all 16 patients followed for a minimum of 1 year were Visick grade I or II. All patients, when directly asked, responded that the operation had been a success and that their reflux symptoms had been improved significantly or abolished by the operation. By comparison, 129 (91 per cent) of 142 and 125 (91 per cent) of 138 patients with proven GORD were Visick grade I or II at 6 months and 1 year respectively (*Table 3*).

Four of the 19 patients required a single successful balloon dilatation for dysphagia between 3 weeks and 7 months after operation. By comparison 22 (15 per cent) of 148 patients with proven GORD underwent at least one balloon dilatation for dysphagia after operation. One patient with ASO who was Visick grade IV at 6 weeks after surgery had dysphagia. She was treated successfully by balloon dilatation and was Visick grade II at 6 months after operation. Two patients were Visick grade III at 6 weeks after operation and one remained Visick grade III at 6 months owing to dysphagia. Both underwent balloon dilatation and were Visick grade II following this. There were two late complications, both acute mediastinal wrap hernias, which occurred at 12 and 17 months after operation. Both patients underwent open reduction and repair.

Discussion

The outcome of antireflux surgery in patients with physiological levels of acid exposure on preoperative 24-h

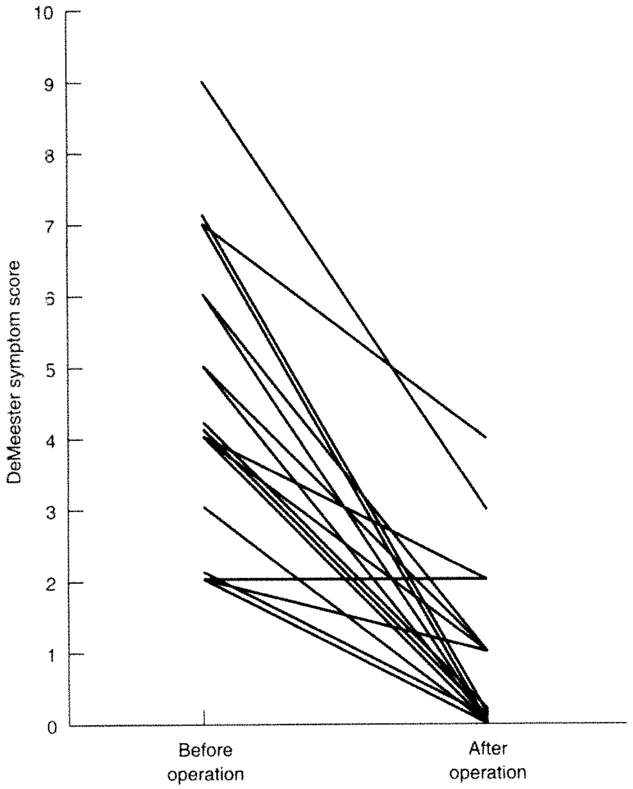

Fig. 1 DeMeester symptom scores before and 1 year after operation ($n = 19$). $P < 0{\cdot}001$ (Mann–Whitney rank sum test)

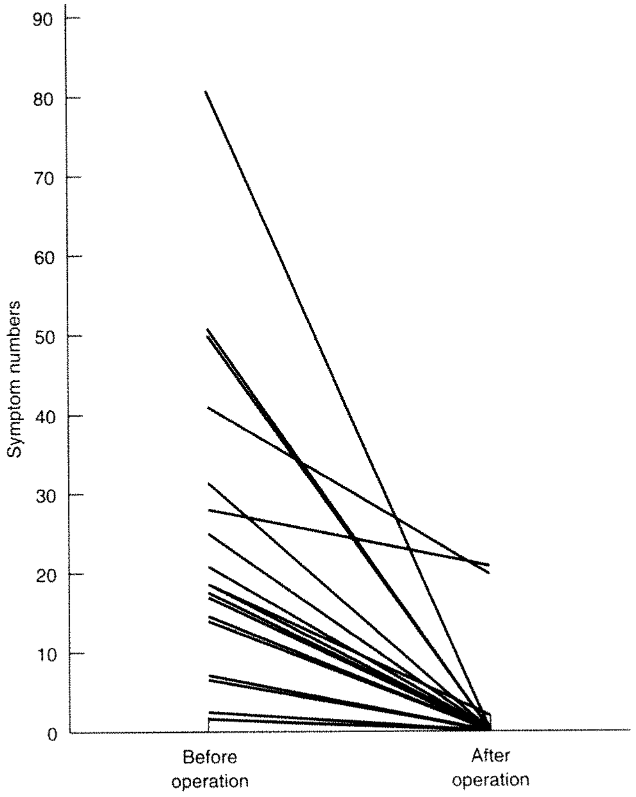

Fig. 2 Preoperative and postoperative numbers of symptom events on 24-h pH tests ($n = 19$). Preoperative values are means of two pH tests. $P < 0{\cdot}001$ (Mann–Whitney rank sum test)

Table 3 Postoperative Visick scores in patients with acid-sensitive oesophagus and gastro-oesophageal reflux disease

	6 weeks		6 months		1 year	
Visick score	ASO	GORD	ASO	GORD	ASO	GORD
I	6 (32)	72 (49)	9 (47)	80 (56)	9 (56)	86 (62)
II	10 (53)	64 (43)	9 (47)	49 (35)	7 (44)	39 (28)
III	2 (11)	11 (7)	1 (5)	13 (9)	0 (0)	9 (7)
IV	1 (5)	1 (1)	0 (0)	0 (0)	0 (0)	4 (3)
Total	19	148	19	142	16	138

Values in parentheses are percentages. ASO, acid-sensitive oesophagus; GORD, gastro-oesophageal reflux disease

pH tests has recently been reported as being inferior to that of patients with proven GORD[16]. However, the multivariate analysis performed by Campos *et al.* did not include an assessment of the correlation between patients' symptoms and acid reflux events on 24-h pH tests. The failure to confirm such an association before operation may explain why 35 per cent of their 'non-GORD' patient subgroup reported 'fair' or 'poor' results of surgery. The study reported here is the first to examine the outcome of antireflux surgery in a clearly defined group of patients with ASO, based on endoscopic, pH and symptom index criteria.

The concept of the ASO is not new, having been introduced in a number of studies in the past 10 years[4–6,17,18]. A clear definition of what constitutes an ASO has, however, been slow to appear. The present authors have taken the term to indicate a patient who has no endoscopic oesophagitis and normal distal oesophageal acid exposure confirmed on repeat 24-h pH-metry, but a positive (i.e. more than 50 per cent) correlation between symptoms and episodes of acid reflux. This definition exceeds that used in previous reports[4–6], and is therefore less likely to include patients who in fact have pathological levels of gastro-oesophageal reflux.

The parameters used to determine normal distal oesophageal acid exposure will influence the diagnosis of ASO against that of 'pathological' GORD. If the normal cut-off values are raised then ASO will be diagnosed more frequently. Despite several large studies in healthy controls and symptomatic patients[19,20], there is no widespread agreement on what constitutes a 'normal' 24-h pH study. Strict criteria (less than 6 per cent of upright time, less than 2 per cent of supine time and less than 4 per cent of total time) were employed in the present study in order to avoid overdiagnosis of ASO in patients who may have true pathological reflux. By comparison, ASO has been defined variously by an AET of less than 6·95 per cent[4], below 5 per cent[6] and less than 4·2 per cent[5].

Up to 30 per cent of symptomatic patients with an initially normal 24-h pH test will have an abnormal repeat test[19–22], particularly if the patient has little in the way of their typical reflux symptoms on the first test day[23]. This implies that a proportion of patients given a diagnosis of ASO on the basis of a single 24-h pH test may in fact have pathological levels of oesophageal acid exposure if tested on a more symptomatic day. Previous reports have not required repeat pH tests to establish a diagnosis of ASO and thus may over-report the condition.

This protocol stipulated that patients should have no endoscopic evidence of oesophagitis. By comparison, oesophagitis was recorded in 18 per cent[4] of Trimble *et al.*'s and 19 per cent[5] of Shi *et al.*'s patients with ASO. Furthermore, in the latter study 37 per cent had a hiatus hernia. All of the present patients had received antireflux medication from the general practitioner or referring physician before preoperative endoscopy. Although such medication was discontinued for at least 7 days before endoscopy, some patients might have had oesophagitis before treatment that had subsequently healed.

A variety of methods may be employed to categorize an acid reflux episode and to determine whether a symptom event is related causally to an individual reflux episode. Watson *et al.*[6] regarded a symptom event as reflux related if it occurred coincidentally or within 2 min of a fall in pH to below 4. Trimble *et al.*[4] also required the pH to fall below 4 but used a 5-min window after each reflux episode. Both groups took a symptom index of 50 per cent or greater to be positive. Shi *et al.*[5] additionally calculated the symptom sensitivity index and the probability that symptoms and reflux episodes occurred by chance, taking $P < 0.05$ as significant. The present investigation used a symptom index analysis similar to that employed by the Utrecht group[13], i.e. a fall in distal oesophageal pH of 1·5 units from a steady level, regardless of whether the pH falls below 4, and an event window that starts at the onset of the reflux episode and ends 2 min after its cessation. This recognizes the finding of Shi *et al.*[5] that reflux episodes perceived by patients with ASO tend to have a higher minimum pH and shorter duration than those of patients with true GORD.

It is important to distinguish between ASO and the term 'irritable oesophagus'. Irritable oesophagus is a term applied in the setting of a patient with non-cardiac chest pain and implies that oesophageal sensory thresholds have been determined using intraoesophageal balloon distension or provocation tests with acid or edrophonium[24,25].

The H_2-receptor antagonist famotidine has been shown to reduce oesophageal sensitivity to acid exposure in endoscopy-negative GORD[26], but its effect on the ASO has not been reported. In this context, all of the present patients underwent surgery because of incomplete success of medical therapy.

A placebo effect of surgery cannot be ruled out entirely. The only truly objective assessments possible in these largely asymptomatic postoperative patients were the highly significant falls in the mean number of reflux episodes on 24-h pH-metry and total AETs. The Visick scores at 1 year compared favourably with those in a contemporary group of patients undergoing antireflux surgery for pathological levels of gastro-oesphageal reflux and with those in the literature[3], suggesting that patients with ASO achieve equally good symptomatic relief through surgery. By this time any placebo effect would be expected to have revealed itself. Longer-term follow-up, including quality of life assessment, will help to clarify this issue.

The comparatively high rate of postoperative balloon dilatation partly reflects the authors' predilection for treating patients with dysphagia in this way. The dilatation rate did not differ significantly from that seen in a series of patients with pathological levels of gastro-oesophageal reflux. Two of the four patients with ASO who had balloon dilatation were adolescents (aged 12 and 14 years; dilated once each at 3 weeks). In these patients, early postoperative dysphagia is an emotive as well as a physiological problem, causing distress and concern to patients and parents alike. As a result the authors are more likely to perform early dilatation on adolescents with dysphagia, whilst employing a more expectant policy with adults.

In conclusion, a combination of endoscopy, repeat 24-h pH testing and symptom index analysis can define clearly a small but eminently treatable population of patients with the ASO syndrome. In this group, when standard medical management provides inadequate symptom relief, laparoscopic antireflux surgery is a valid and effective treatment.

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Original article

Determinants of death following burn injury

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Background: Burn care has changed considerably. Early surgery, nutritional support, improved resuscitation and novel skin replacement techniques are now well established. The aim of the study was to establish whether changes in management have improved survival following burn injury and to determine the contributory factors leading to non-survival.

Methods: This was a retrospective outcome analysis of data collected from a consecutive series of 4094 patients with burns admitted to a tertiary referral, metropolitan teaching hospital between 1972 and 1996.

Results: The overall mortality rate was 3·6 per cent. This decreased from 5·3 per cent (1972–1980) to 3·4 per cent (1993–1996) ($P = 0·076$). The risk of death was increased with increasing burn size (relative risk (RR) 95·90 (95 per cent confidence interval 12·60–729·47) if more than 35 per cent of the total body surface area was burned; $P < 0·001$) increasing age (RR 7·32 (3·08–17·42) if aged more than 48 years; $P < 0·001$), inhalation injury (RR 3·61 (2·39–5·47); $P < 0·001$) and female sex (RR 1·82 (1·23–2·69); $P = 0·003$). Operative intervention (RR 0·11 (0·06–0·21); $P < 0·001$) and the presence of an upper limb burn (RR 0·53 (0·35–0·79); $P = 0·002$) decreased the risk.

Conclusion: Modern burn care has decreased the mortality rate. Increasing burn size, increasing age, inhalation injury and female sex increased, while operative intervention and an upper limb burn decreased, the risk of death.

Presented to the 10th Congress of the International Society for Burn Injuries, in Jerusalem, November 1998
Paper accepted 14 November 2000
British Journal of Surgery 2001, 88, 583–587

Introduction

Burn injury is very common. It affects approximately 1 per cent of the population each year. The vast majority of these injuries are minor, although quite painful. In contrast, a small number of individuals receive massive deep burns that are accompanied by permanent disfigurement or death. The past few decades have seen many changes to burn care that have decreased the frequency of patient morbidity and death. Oliguric renal failure subsequent to burn shock, uncontrolled burn wound infection and postburn contractural deformities were once common among burn victims. These entities are now quite uncommon. This study examined the effect that these changes have had on rates of survival following burn injury and the factors that increase the risk of death among patients treated at a tertiary burn referral centre.

Patients and methods

The details of patients admitted to the burn service of the Royal Brisbane Hospital since 1972 have been recorded in an electronic database. Data have been collected prospectively since 1990. A paper registry was kept and the medical records were reviewed after approval by the Institutional Ethics Committee. An Access^{TM} program (Microsoft, Sydney, Australia) on a Pentium^{TM} personal computer (NEC, Sydney, Australia) was customized to suit the purpose.

Patients included in the study were greater than 10 years of age and were treated during the period 1972–1996. Data collected included age, sex, burn depth and size, cause of injury, year of admission, length of hospital stay, operative intervention, presence of smoke inhalation injury, anatomical distribution of burn and outcome.

To allow changes in mortality trends over time to be shown, year of admission was grouped into the intervals before 1980, 1981–1984, 1985–1988, 1989–1992 and 1993–1996. Burn size was also grouped into 2 per cent or less, 3–5 per cent, 6–10 per cent, 11–20 per cent, 21–35 per cent and more than 35 per cent of the total body surface area (TBSA). These intervals were defined in order to gain an even distribution of patient numbers in each group, while retaining a large enough number of groups to allow comparison of trends.

Statistical analysis

Determinant factors considered in this multivariate analysis were age, burn size (TBSA), presence of smoke inhalation injury, sex, performance of burn wound excision and operative intervention (skin grafting), anatomical site of burn, year of admission and cause of burn. Several statistical models were considered. A probit model was rejected as the distribution of mortality against burn size was not strongly sigmoidal, an assumption underlying valid use of the probit model (*Fig. 1*). A logistic regression model assumes equal length of follow-up and was not considered appropriate as length of hospital stay was highly variable. The Cox proportional hazards regression model, which is in the same generalized linear models as logistic regression, was chosen as it allows estimates of survival and relative survival between levels of any factor to be derived. All analyses were performed using SPSS version 7.5 statistical package (SPSS, Chicago, Illinois, USA) on an IBM personal computer (IBM, Sydney, Australia). Statistical significance was defined at the 95 per cent level (two-tailed). The precision of estimated relative survival rates was expressed by quoting 95 per cent confidence intervals.

Results

A total of 4094 patients were admitted for acute burn injury during the study period of whom 146 (3·6 per cent) died. Three-quarters of the patients were male. Patients' ages ranged from 10 to 97 (median 29) years; half were aged between 10 and 30 years (*Fig. 2*).

The major cause of injury was flame related (43·8 per cent) and scalding (24·5 per cent) was the next most frequent. Contact, chemical, electrical and friction burns were responsible for a further 23·5 per cent of injuries. More than half had burns to less than 6 per cent of the TBSA while 26 patients (0·9 per cent) suffered burns to greater than 90 per cent of the TBSA. Burns were located on the upper limbs in 51·4 per cent, lower limbs in 39·8 per cent and on the head in 29·4 per cent. Burns to the trunk were present in 29·4 per cent of patients and genital burns were present in 6·5 per cent. Multiple sites of injury were frequently present. The incidence of inhalation injury was 4·0 per cent. Operative intervention was noted in 24·1 per cent.

Age, sex, year of admission, burn size, inhalation injury, operative intervention, and injuries to the upper limbs, head or trunk when taken as independent variables all significantly influenced the mortality rate ($P < 0{\cdot}001$). Multivariate analysis of the individual prognostic factors showed that the determinants of death were increasing age and burn size, inhalation injury and female sex (*Table 1*). The mortality rate was decreased by operative intervention or if the burn was sited on the upper limb (*Table 2*). Year of admission approached, but did not achieve, a significant decrease in mortality rate ($P = 0{\cdot}076$) once the other concurrent factors were taken into account (*Table 3*).

The strongest independent determinant of death in burns patients was burn size ($P < 0{\cdot}001$). The relative risk of death was lowest for patients sustaining a burn of less than 2 per cent of the TBSA. A steady increase in mortality rate was noted with increasing burn size. Patients with a burn size of greater than 35 per cent of the TBSA had a 95·9 (95 per cent confidence interval 12·60–729·47) times greater risk of death than those with a burn affecting 2 per cent or less of the TBSA.

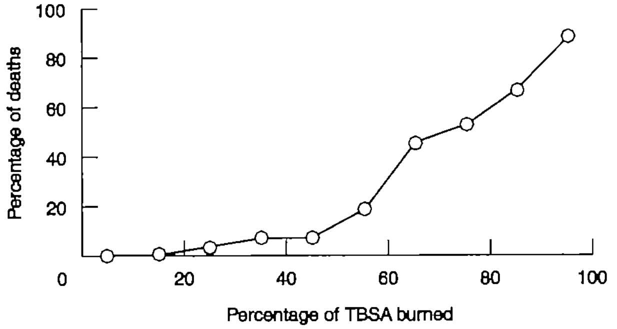

Fig. 1 Deaths in relation to burn size. Large burns caused more deaths, but the distribution was not strongly sigmoidal leading to rejection of probit analysis. TBSA, total body surface area

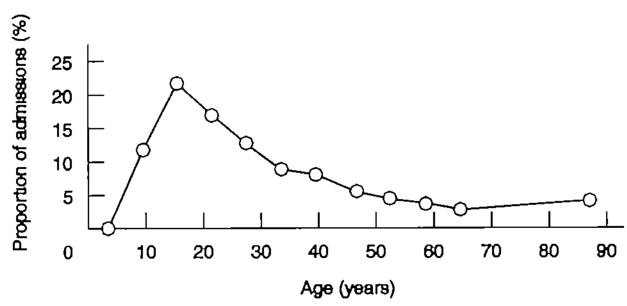

Fig. 2 Distribution of age. Half of the patients were aged between 10 and 30 years

Table 1 Factors increasing risk of death

	Relative risk	P
Burn size (%TBSA)		
<2	1·00	<0·001
2–4	1·87 (0·19–18·09)	
5–9	1·36 (0·12–15·20)	
10–19	6·60 (0·82–53·34)	
20–34	17·77 (2·26–139·51)	
≥35	95·88 (12·60–729·47)	
Age (years)		
1–20	1·00	<0·001
21–26	1·94 (0·72–5·26)	
27–34	2·76 (1·08–7·06)	
35–48	3·10 (1·25–7·69)	
>48	7·32 (3·08–17·42)	
Inhalation injury		
No	1·00	<0·001
Yes	3·61 (2·39–5·47)	
Sex		
Male	1·00	0·003
Female	1·82 (1·23–2·69)	

Values in percentages are 95 per cent confidence intervals. TBSA, total body surface area

Table 2 Factors decreasing risk of death

	Relative risk	P
Skin graft operation		
No	1·00	<0·001
Yes	0·11 (0·06–0·21)	
Unknown	0·85 (0·40–1·80)	
Upper limb burn		
No	1·00	0·002
Yes	0·53 (0·35–0·79)	

Values in percentages are 95 per cent confidence intervals

Table 3 Burn mortality rate 1972–1996

Admission year	No. of patients	Mortality rate (%)	Relative risk
1972–1980	1037	5·3	1·00
1981–1984	672	3·3	0·61 (0·34–1·09)
1985–1988	828	2·3	0·56 (0·22–1·42)
1989–1992	821	3·0	1·09 (0·45–2·60)
1993–1996	736	3·4	1·18 (0·51–2·70)*
Total	4094	3·6	

Values in percentages are 95 per cent confidence intervals. *$P = 0{\cdot}076$ (Cox proportional hazards test)

Age was seen to be a determinant of death on both individual and multivariate analysis ($P < 0{\cdot}001$). The mortality rate was lowest for patients under the age of 20 years. The risk of death following burn injury increased with age; patients over the age of 48 years were 7·3 times more likely to die following a burn injury. Inhalation injury increased the risk of death 3·6-fold. ($P < 0{\cdot}001$). The mortality rate was increased 1·8-fold among females ($P = 0{\cdot}003$). This was evident in both individual and multivariate analysis.

The presence of burns to the upper limbs, but no other anatomical site, was associated with a decreased risk of death on multivariate analysis ($P = 0{\cdot}002$). Operative intervention decreased the risk of death by almost 90 per cent ($P < 0{\cdot}001$), although it should be noted that data were not available for one-third of the sample. The cause of the injury had no effect on outcome ($P = 0{\cdot}34$).

Discussion

Burn injury can be devastating even if it involves only a small area. A deep burn to the face or hands creates major cosmetic and functional disabilities. The purpose of this study was to examine the effect that the many changes in burn care over the past few decades have had on survival and to identify the factors that make death from burns more likely. A number of techniques to predict the likelihood of death following burn injury have been described. These include scoring systems such as the 'Baux Rule' and the 'Abbreviated Burn Severity Index' of Tobiasen, probit analysis, logistic regression analysis and proportional hazards[1–6].

Ryan and colleagues[7] analysed the outcome of 1665 patients treated between 1990 and 1996. They sought to develop a simple method of prediction of risk of death based on objective clinical criteria available at the time of admission. The mortality rate was 4 per cent. Three risk factors for death were identified: age over 60 years, burn size greater than 40 per cent of the TBSA and presence of smoke inhalation injury. The mortality rate rose from 0·3 per cent if no risk factor was present to 3 per cent for one, 33 per cent for two and to 90 per cent if all three risk factors were present. In contrast to the present data, sex did not alter survival rates once burn size, age and inhalation injury were considered. The limitations of Ryan's simple predictive formula become apparent when one considers that a young person with a 100 per cent TBSA burn and no inhalation injury should have only a 3 per cent risk of death, a point supported by Saffle[8]. Coste and colleagues[9] produced an even simpler predictive formula, calculating a score as 2 (age − 50) + percentage TBSA for age greater than 50 years, or percentage TBSA otherwise. Smith *et al.*[10] and Saffle and Colleagues[11] have published the outcome of 1447 and 6417 patients respectively, and both acknowledge the lethality of smoke inhalation when combined with burn injury. Saffle *et* *al.* reported pooled data from 28 burn centres who proffered results to the American Burn Association Patient Registry between 1991 and 1993. The overall mortality rate was 4·1 per cent, which rose to 29·4 per cent in the group with inhalation injury. Smith *et al.* reported almost identical figures.

While it is gratifying to note that the mortality rate has decreased in the present study and is at an acceptable level, these statistics cannot tell the whole story. While virtually all children and adolescents can be salvaged from even the most devastating burn and live to enjoy fruitful and productive lives, there is a small group whose concomitant injuries, such as hypoxic brain damage, leads one to question whether survival is the most desirable outcome. Bland statistics and predictive formulae also do not account for comorbidities that may exist in the individual. The unfortunate individual whose cerebral metastasis caused him to collapse on the stove may well succumb even though the burn was minor. Therefore, although survival scores and formulae remain useful tools for purposes of audit and comparison, they should not be applied to the individual. In this respect the authors are in agreement with Choiniere *et al.*[12].

Female sex was shown to be a significant predictor of death among this patient sample as in other studies[13,14]. Sex differences in the thickness of skin and in the proportion of body fat to muscle mass between men and women may be responsible. Another explanation may lie in the fact that a significant percentage of the largest burns were self-inflicted, in the majority of cases by women. These burns are often very extensive and quite deep, making survival less likely. The presence of an upper limb burn reduced the mortality rate. While small burns commonly affect the upper limb, burns to this area are often not as deep as those elsewhere because scalds and flash burns are over-represented. This may, in part, explain this curious finding.

Modern burn care is driven by the philosophy of undertaking activities that will attenuate the systemic inflammatory response[15,16]. These include control of wound infection with topical antimicrobials (1970s), enteral nutrition (1980), adequate pain relief, early surgery (late 1980s), use of anabolic agents and beta blockade (1990s), and use of artificial/cultured skin where appropriate (late 1990s)[17–26]. These activities are best undertaken in burn centres staffed by individuals well versed in meeting the complex, competing challenges that a severely burned person provides. The Australian and New Zealand Burn Association has developed guidelines, espoused in the Emergency Management of Severe Burns course, to aid in the selection of appropriate patients for referral to a burn centre (*Table 4*).

Table 4 Referral guidelines

Burns greater than 10 per cent of total body surface area
Burns of special areas: face, hands, feet, genitalia, perineum, over major joints
Full-thickness burns greater than 5% of TBSA in adults and 2% of TBSA in children
Electrical burns
Chemical burns
Burns with an associated inhalation injury
Circumferential burns of the limbs or chest
Burns at the extremes of age, in children and the elderly
Burn injury in patients with pre-existing medical disorders that could complicate management, prolong recovery or effect mortality rate
Any burn patient with associated trauma
Burns associated with self-harm or assault

Optimum outcomes should result from appropriate early referral to a burn centre. TBSA, total body surface area

Increasing burn surface area, increasing age, the presence of a respiratory burn/inhalation injury, absence of a skin graft procedure and female sex all significantly increased the risk of death. The overall mortality rate continues to decline principally owing to more rapid wound closure.

Acknowledgements

The authors thank Diana Battistuta, Biostatistician, and Karin Kaiser, Database Manager. This work was supported by the Motor Accident Insurance Commission (QLD)–Royal Australasian College of Surgeons Trauma Fellowship.

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Original article

Leptin and its relation to weight loss, *ob* gene expression and the acute-phase response in surgical patients

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Background: Patients with cachexia suffer from anorexia, weight loss and hypermetabolism. This study examined the relationship between plasma leptin concentration, leptin gene expression, weight loss and the acute-phase response in a group of surgical patients.

Methods: Body composition, plasma leptin, interleukin (IL) 6, soluble tumour necrosis factor receptor (sTNF-R) 55, sTNF-R75 and C-reactive protein were analysed in a cohort of 28 patients undergoing elective surgery. Subcutaneous and omental leptin messenger RNA (mRNA) was analysed in a subgroup of 14 patients.

Results: After adjustment for fat mass (FM), a significant partial correlation coefficient was found between plasma leptin and serum IL-6 concentration ($P = 0.037$). A positive correlation was found only between plasma leptin and omental leptin mRNA ($P = 0.009$). Patients with an acute-phase response had a significantly higher level of plasma leptin per unit FM ($P = 0.049$). Stepwise multiple regression showed that FM ($P < 0.0005$) and serum IL-6 ($P = 0.018$) were independent predictors of plasma leptin level.

Conclusion: Plasma leptin levels appear to be influenced by proinflammatory cytokines. Omental fat may have more influence on plasma leptin than subcutaneous fat. Accelerated weight loss in patients with cancer with an ongoing inflammatory response could be mediated in part by inappropriately high plasma levels of leptin.

Paper accepted 5 December 2000

British Journal of Surgery 2001, 88, 588–593

Introduction

Leptin, the adipocyte-derived product of the antiobesity gene, continues to attract considerable interest[1,2]. In mice, leptin appears to act as a hormonal signal in the afferent limb of a negative feedback loop between adipose tissue and the feeding centres in the hypothalamus[3,4]. Upon deposition of fat, the plasma leptin level rises, hypothalamic leptin receptors are activated[5] and neuropeptide Y levels in the ventromedial nucleus decrease[6], with consequent appetite reduction and a simultaneous increase in metabolic rate[7,8]. In addition, serum cytokines may upregulate leptin levels, suggesting that cytokine-mediated anorexia may, in part, be mediated through leptin[9,10].

Human studies have demonstrated a strong association between plasma leptin levels and adiposity in obese, normal weight[11] and weight-losing individuals[12]. Administration of cytokines to human volunteers has been followed by an increase in leptin levels[13,14].

Cachexia is a debilitating syndrome of weight loss, anorexia and hypermetabolism, found in many patients with advanced cancer or chronic inflammatory diseases, which is accompanied by decreased quality of life[15] and survival[16,17]. Increased production of leptin has been suggested as a possible mediator of the cachectic process. However, in a study of lung cancer cachexia, individuals with detectable plasma leptin levels had less weight loss and greater fat mass (FM)[18], while in a group of patients with gastrointestinal cancer plasma leptin concentration was related to the predicted percentage body fat and was not raised in the presence of an inflammatory response[12]. None the less, in patients with weight loss due to emphysema, the serum leptin level did correlate with serum soluble tumour necrosis factor receptor (sTNF-R) 55 when adjusted for FM[19].

In an attempt to resolve the controversy regarding the role of leptin in cachexia, the relationship between leptin, weight loss and the inflammatory response in a group of elective colorectal surgical patients, divided into those with and those without weight loss, was examined. As previous work had highlighted differences in leptin production between the omental and subcutaneous compartments, leptin messenger RNA (mRNA) expression was analysed in a consecutive subgroup of patients in order to compare leptin gene expression in the two fat compartments between weight-losing and weight-stable patients.

Materials and methods

Patient population and study protocol

A cohort of 28 patients (age range 45–91 years) undergoing colorectal surgery for colorectal cancer or diverticular disease formed the study population. None of the patients suffered from bowel obstruction. Patients were interviewed and consented the day before surgery. Height and weight was measured and the degree of weight loss recorded. After an overnight fast, a blood sample (15 ml) was obtained for analysis of leptin, C-reactive protein (CRP), interleukin (IL) 6, sTNF-R55 and sTNF-R75. In a subgroup of 14 patients, biopsies were obtained at the start of surgery and without the use of diathermy from the abdominal wound subcutaneous fat and from the greater omentum. Biopsies were snap-frozen in liquid nitrogen using Wollenberger tongs and stored at –70°C until subsequent analysis of leptin mRNA. The study was approved by the Lothian Research Ethics Committee.

Body composition

Body height was measured to the nearest 0·5 cm with the patient standing barefoot. Body-weight was measured to the nearest 0·1 kg with the patient barefoot and wearing light clothing. Body mass index (BMI) was calculated using the formula BMI = weight (kg)/(height (m))^2. Predicted total body water (TBW) in litres was derived from validated standard equations[20] based on sex, age (years), height (centimetres) and weight (kilograms). For female patients, $\text{TBW} = -2{\cdot}097 + (0{\cdot}1069 \times \text{height}) + (0{\cdot}2466 \times \text{weight})$. For male patients, $\text{TBW} = 2{\cdot}447 - (0{\cdot}09516 \times \text{age}) + (0{\cdot}107 \times \text{height}) + (0{\cdot}3362 \times \text{weight})$. Fat-free mass (FFM) in kilograms was determined using the following formula: $\text{FFM} = \text{TBW}/0{\cdot}73$. FM was calculated as follows: FM = total body-weight – FFM.

Blood analysis

Blood was drawn in evacuated collection tubes. Serum samples were collected in 10-ml Monovette® Serum Gel tubes (Sarstedt, Numbrecht, Germany) and plasma samples were collected in 5-ml ethylenediamine tetra-acetic acid tubes (Sarstedt). Plasma and serum samples were stored at –70°C until analysis.

Leptin

Plasma leptin was measured by radioimmunoassay as described elsewhere[21] using a commercial kit (Human Leptin RIA kit; Linco Research, St Charles, Missouri, USA). The limit of sensitivity was 0·5 µg/l.

Interleukin, C-reactive protein and tumour necrosis factor receptor

Serum IL-6, CRP, sTNF-R55 and sTNF-R75 were all measured by indirect enzyme-linked immunosorbent assay. IL-6 was measured using a monoclonal antihuman IL-6 antibody and peroxidase-conjugated fragments for antigen binding of a murine monoclonal antihuman IL-6 antibody (CLB, Amsterdam, The Netherlands). The lower limit of detection was 5 pg/ml. CRP was measured using rabbit antihuman CRP antibody and peroxidase-conjugated rabbit antihuman CRP antibody (DAKO, High Wycombe, UK). The lower limit of detection was 1 mg/ml. sTNF-R55 and sTNF-R75 were measured using polyclonal and monoclonal anti-sTNF-R55 and anti-sTNF-R75 antibodies kindly provided by Dr W. A. Buurman, University of Maastricht, The Netherlands[19]. The lower limit of detection was 190 pg/ml for sTNF-R55 and 2 ng/ml for sTNF-R75. In all cases a standard curve was constructed from standards provided by the suppliers. The coefficient of variation for all plasma assays was below 10 per cent.

Leptin messenger RNA analysis

Total RNA was extracted from adipose tissues using TRIzol™ reagent according to the method described by the manufacturer (Life Technologies, Paisley, UK). Hypoxanthine–guanine phosphoribosyl transferase (HPRT) mimic DNA was prepared as described in the PCR Mimic™ construction kit (Clontech Laboratories, Basingstoke, UK). Mimic DNA was constructed for the quantification of leptin complementary DNA (cDNA) using a 574-base pair neutral DNA fragment and composite primers as described by the manufacturer (Clontech Laboratories). The composite primers contained a neutral DNA-specific sequence and a leptin (target) DNA-specific primer sequence. This polymerase chain reaction (PCR) product was the leptin mimic DNA. Each 50-µl PCR reaction contained 0·5 ng neutral DNA, 50 pmol of each PCR primer, 200 mmol/l of each deoxyribonucleoside 5′-

triphosphate, magnesium chloride 3 mmol/l, potassium chloride 500 mmol/l, Tris-HCl 100 mmol/l, pH 8·3 and 0·25 units of Ampli Taq Gold DNA polymerase. The conditions used for the PCR were 94°C for 10 min followed by 30 cycles at 65°C for 1 min, 72°C for 2 min and 94°C for 1 min. The products of the PCR reaction were separated by electrophoresis at 80 V in a 2 per cent (w/v) low melting point agarose gel and the resulting band was excised from the gel and purified using the Wizard™ PCR Preps DNA purification kit (Promega, Southampton, UK). A 1-µl sample of purified leptin mimic DNA was reamplified by PCR as described above but using target primers (50 pmol). The resulting reamplified leptin mimic DNA was isolated from the primers as described above. The concentration in attamoles per microlitre of the mimic DNA was determined following spectrophotometric analysis. In order to quantify the amount of each target, 1 µl of cDNA sample was added to reaction mixtures containing different concentrations of mimic DNA. To each reaction mixture, target primers for leptin cDNA (50 pmol primer) and for HPRT cDNA (1 pmol primer) were added along with the rest of the components required for PCR. The volumes of these components and the conditions used for PCR were as before. Quantification of the amount of PCR products from mimic and target DNA was carried out by densitometry on a GelDoc 2000 system (BioRad Laboratories, Hemel Hempstead, UK). The ratio of optical density of mimic DNA and target cDNA PCR products was calculated and plotted against the known concentration of mimic DNA. In order to compensate for the differences in the size of the PCR products of mimic DNA and target cDNA, the concentrations of leptin cDNA were multiplied by 1·63 and the concentrations of HPRT cDNA were multiplied by 1·91. Each constant value was derived from the ratio of the sizes of mimic DNA and target cDNA PCR products. In order to eliminate variations between samples, the ratios of the concentration of leptin cDNA and HPRT cDNA were determined.

Statistical analysis

Mann–Whitney *U* test was used for comparison of interval data between individual groups and Wilcoxon signed rank test for comparison of related interval data. Measures of association were performed using Spearman's rank correlation test. The association between leptin and IL-6 while controlling for FM was calculated using partial correlation after logarithmic transformation of the data. In patients with IL-6, CRP and sTNF-R75 values below the detectable limit (5 pg/ml, 1 mg/l and 2 ng/ml respectively), the values 5 pg/ml, 1 mg/l and 2 ng/ml respectively were used in the analysis. A stepwise multiple regression model was used to define factors responsible for variations in plasma leptin levels. Data in the text are expressed as median (range). Significance was determined at the 5 per cent level. All statistical calculations were performed using the SPSS statistical package (SPSS, Chicago, Illinois, USA).

Results

Twenty-eight patients were enrolled in the study of whom 22 had colorectal cancer and six had diverticular disease. Patient demographic data and blood analyses are presented in *Table 1*. Patients were divided into two subgroups, weight stable (*n* = 13) and weight losing (*n* = 15). There were nine patients with cancer in the weight-stable group and 13 in the weight-losing group. Weight-losing patients had lost 13·3 (5·7–47·6) per cent of their preillness body-weight. Percentage weight loss in patients with malignant disease (13·3 (5·7–47·6) per cent) was similar to that in patients with benign disease (13·6 (10·5–16·7) per cent) (*P* = 0·734).

Table 1 Patient characteristics

	Male			Female		
	Weight stable (*n*=6)	Weight losing (*n*=8)	*P**	Weight stable (*n*=7)	Weight losing (*n*=7)	*P**
Weight loss (%)		11·1 (6·2–24)			19·7 (5·7–47·6)	
Body mass index (kg/m^2)	28·0 (22·8–26·3)	24·5 (17·6–28·1)	0·070	22·9 (16·4–35·9)	19·3 (15·1–27·9)	0·110
Fat mass (kg)	24·5 (18·1–31·4)	16·9 (6·8–26)	0·028	20·3 (8·7–35·3)	12·2 (3·7–24·0)	0·048
IL-6 (pg/ml)	5·0 (5·0–5·0)	6·1 (5·0–10)	0·052	6·4 (5·0–17·8)	5·0 (5·0–28·5)	0·838
CRP (mg/l)	2·0 (2·0–9·9)	3·8 (2·0–54·3)	0·408	3·4 (2·0–27·9)	2·0 (2·0–109·4)	0·842
sTNF-R55 (ng/ml)	1·2 (1–2·1)	1·6 (1·1–6·9)	0·156	1·5 (0·9–3·3)	2·0 (0·4–3·9)	0·848
sTNF-R75 (ng/ml)	1·0 (1·0–3·9)	2·6 (1·0–16·1)	0·270	1·0 (1·0–6·9)	2·6 (1·0–6·9)	0·453
Leptin (ng/ml)	7·0 (4–29·3)	4·0 (0·9–12·7)	0·302	24·7 (2·1–51·5)	3·2 (1·4–39·7)	0·085

Values are median (range). IL, interleukin; CRP, C-reactive protein; sTNF-R, soluble tumour necrosis factor receptor. *Mann–Whitney *U* test

Weight-losing patients had a significantly lower plasma leptin level than weight-stable patients (3·9 (0·9–39·7) *versus* 11·4 (2·1–51·5) ng/ml; P = 0·038). The plasma leptin level was inversely related to percentage weight loss (Spearman's ρ = −0·523, P = 0·004). The plasma leptin level tended to be lower in male than in female patients but the difference did not reach statistical significance (4·5 (0·9–29·3) *versus* 9·4 (1·4–51·5) ng/ml; P = 0·301). Patients with malignant disease tended to have lower plasma leptin levels than those with benign disease but this was not significant (4·4 (0·9–51·5) *versus* 17·8 (3·2–29·3) ng/mL; P = 0·124).

The plasma leptin level correlated with BMI (Spearman's ρ = 0·570, P = 0·002) and FM (Spearman's ρ = 0·624, P < 0·001). After adjustment for FM as a possible confounder, a significant partial correlation coefficient was found between plasma leptin and serum IL-6 (r = 0·4035, P = 0·037) but not between plasma leptin and serum sTNF-R55 (r = −0·0342, P = 0·866) or serum sTNF-R75 (r = −0·066, P = 0·742).

Leptin mRNA levels in subcutaneous fat were almost ten times higher than those in omental fat (10·7 (0·31–34·4) *versus* 1·1 (0·1–9·4); P = 0·002). A significant positive correlation was found between plasma leptin level and omental leptin mRNA (Spearman's ρ = 0·666, P = 0·009) but not between plasma leptin level and subcutaneous leptin mRNA (Spearman's ρ = 0·246, P = 0·396). Moreover, omental leptin mRNA correlated significantly with body FM (Spearman's ρ = 0·785, P = 0·001) and BMI (Spearman's ρ = 0·629, P = 0·016). In contrast, there was no significant correlation between subcutaneous leptin mRNA and FM (Spearman's ρ = 0·273, P = 0·345) or BMI (Spearman's ρ = 0·251, P = 0·387). Omental leptin mRNA was significantly lower in weight-losing patients than in weight-stable patients (P = 0·004) (*Table 2*). No significant difference was found in subcutaneous leptin mRNA between weight-stable and weight-losing patients (P = 0·949).

Patients who exhibited an acute-phase response (defined as CRP level of 10 mg/ml or more) had a significantly lower FM (P = 0·018), a similar plasma leptin level (P = 0·793) but a significantly higher plasma leptin level per unit FM (P = 0·049) than patients without an acute-phase response (*Table 3*). Serum IL-6 was significantly higher (P = 0·007) and there was a trend towards a higher level of sTNF-R55 (P = 0·053) in patients with an acute-phase response.

Stepwise multiple regression showed that FM (P < 0·0005) and serum IL-6 concentration (P = 0·018) were the only two independent predictors of plasma leptin level with correlation values of 0·398 and 0·520 respectively. sTNF-R55 (P = 0·730) and sTNF-R75 (P = 0·530) were excluded from the regression model as they did not contribute significantly to its predictive value.

Discussion

Plasma leptin concentration usually reflects the total amount of fat present in the body. Among normal, obese and even cachectic patients, plasma leptin levels are strongly related to adiposity and lower plasma leptin levels have been reported consistently among weight-losing patients[12,19,22]. It is therefore not surprising that in the present study plasma leptin levels in both the weight-stable and weight-losing patients were found to correlate directly with BMI and FM, and inversely with percentage weight loss. The lack of any

Table 2 Plasma leptin and leptin messenger RNA expression in subcutaneous and omental fat in patients undergoing colorectal surgery

	Weight stable (n=7)	Weight losing (n=7)	P*
Sex ratio (M : F)	1 : 6	5 : 2	
Plasma leptin (ng/ml)	24·7 (4·7–51·5)	5·3 (1·2–19·7)	0·018
Omental mRNA (units)	4·0 (0·8–9·4)	0·5 (0·1–1·4)	0·004
Subcutaneous mRNA (units)	8·4 (5·9–34·4)	13·9 (0·3–29·7)	0·949

Values are median (range). mRNA, messenger RNA. *Mann–Whitney U test

Table 3 Acute-phase response and plasma leptin concentration in patients undergoing colorectal surgery

	No acute-phase response (n=24)	Acute-phase response* (n=4)	P†
Sex ratio (M : F)	13 : 11	1 : 3	
Body mass index (kg/m^2)	25·1 (16·4–35·9)	18·3 (15·1–22·1)	0·015
Fat mass (kg)	21·6 (6·5–35·3)	9·5 (3·7–17·6)	0·018
IL-6 (pg/ml)	5·0 (5·0–17·8)	11·2 (6·5–28·5)	0·007
sTNF-R55 (ng/ml)	1·4 (0·4–6·9)	1·9 (1·6–3·9)	0·053
sTNF-R75 (ng/ml)	1·0 (1·0–16·1)	4·0 (1·0–8·3)	0·131
Leptin (ng/ml)	5·1 (0·9–51·5)	11·9 (1·8–24·7)	0·793
Leptin/fat mass (ng per ml per kg)	0·3 (0·1–2·5)	1·0 (0·5–1·6)	0·049

Values are median (range). *Inflammatory response with C-reactive protein level 10 mg/l or more. IL, interleukin; sTNF-R, soluble tumour necrosis factor receptor. †Mann–Whitney U test difference between leptin level in patients with benign and malignant disease indicates that changes in leptin concentration are not disease specific (for instance, related directly to the presence of cancer).

Leptin secretion rates in omental and subcutaneous fat have been studied previously in a group of obese and non-obese women, and were found to be two to three times higher in subcutaneous compared with omental fat on a gram of lipid per gram of tissue basis[22]. Leptin gene expression was approximately twice as high in the subcutaneous compartment as that in the omental compartment. Leptin secretion rates in either fat compartment correlated with serum leptin levels. The greater FM in subcutaneous compared with omental tissue, coupled with the reported higher rate of secretion for subcutaneous fat, implied that most of the serum leptin was derived from subcutaneous adipose tissue.

The results of the present study agree with those for obese and non-obese women[22]. Leptin gene expression was substantially higher in subcutaneous as opposed to omental fat. However, a significant positive correlation was found only between omental fat leptin mRNA and plasma leptin level and not between subcutaneous fat leptin mRNA and plasma leptin level. In addition, there was a significant reduction in leptin mRNA expression in omental fat between weight-stable and weight-losing patients, while there was no difference between subcutaneous fat leptin mRNA levels between these two groups. These findings suggest that fundamental differences in leptin gene expression might exist between omental and subcutaneous fat depots. Such differences may be important to our understanding of the cachectic process and deserve further investigation as there has been no previous work published on *ob* gene expression in cachectic patients[19].

It is interesting that leptin mRNA expression is unchanged during weight loss in the quantitatively most abundant (subcutaneous) fat compartment. It may be that subcutaneous fat secretion rates remain unaltered during cachexia and it is simply the mass of fat remaining which has the greatest influence over plasma leptin levels. Omental leptin mRNA expression, on the other hand, appears far more sensitive to overall changes in energy reserve.

In this study, a significant relation was identified between plasma leptin and serum IL-6 concentration when account was taken for FM. A significant relationship has previously been demonstrated between plasma leptin and serum TNF-α in groups of patients suffering from either chronic obstructive pulmonary disease[19] or diabetes[23]. sTNF-R concentrations have been suggested as an index of tissue TNF production. Thus the lack of correlation between plasma leptin concentration and either sTNF-R55 or sTNF-R75 is somewhat surprising. Taken together these findings suggest a complex regulation of leptin by the inflammatory response.

Leptin is a hormone associated with anorexia and hypermetabolism and it has been suggested that circulating levels may be increased by proinflammatory cytokines in human subjects[13,14]. It has therefore been postulated that the decreased food intake and raised energy expenditure found in patients with cachexia may, in part, be related to inappropriately high levels of leptin in these patients. However, when studying cachectic patients with lung cancer leptin was not detected in the majority of patients with severe weight loss and low FM[18]. It was concluded that raised plasma leptin levels did not contribute to cachexia and, since low plasma leptin was not associated with an increased appetite and decreased energy expenditure, disturbance in the hypothalamic part of the feedback mechanism was hypothesized. In another study of patients with gastrointestinal cancer, when plasma leptin levels were compared between weight-losing patients with or without an acute-phase response (CRP 10 mg/ml or more), no significant difference was found[12]. Again, however, plasma leptin was not always detectable. Furthermore, in both studies, plasma leptin level was not expressed in relation to body fat content (leptin/FM). In this study, plasma leptin was detected in every patient. As the degree of weight-loss was similar in this series to that in the two abovementioned studies, the discrepancy in detection might reflect methodological differences in assaying leptin.

In the present study, when leptin was expressed per unit FM, patients exhibiting an acute-phase response did indeed have a higher level of leptin than those who did not have such a response. This is first evidence to suggest that an inflammatory response may lead to an inappropriately high leptin level and thus contribute to weight loss in cachectic patients.

Overall, circulating leptin seems to be influenced by the amount of fat and proinflammatory cytokines such as IL-6. This raises the hypothesis that activation of proinflammatory cytokines exerts significant effects on leptin plasma levels in humans. Further studies elucidating the interaction between leptin, proinflammatory cytokines and acute-phase proteins might provide important insights into the pathways involved in energy balance regulation in cachexia in humans.

Acknowledgements

The authors thank G. Hill for technical assistance during sample collection and for collection of clinical details of the patients; K. N. Nilaweera, J. Maingay and K. Sangster for technical assistance with PCR, cytokine, cytokine receptor and acute-phase protein analysis; and J. Brennand at AstraZeneca for advice and encouragement.

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The Editors welcome topical correspondence from readers relating to articles published in the Journal. Letters should be no more than 250 words in length and should be typed on A4-sized paper in double spacing

Hypertonic saline attenuates end-organ damage in an experimental model of acute pancreatitis (*Br J Surg* 2000; 87: 1336–40)

Sir

This carefully designed and well executed study demonstrates that bolus hypertonic saline attenuates pancreatic and end-organ injury in experimental acute pancreatitis. Clearly the results carry sufficient weight to justify clinical appraisal. Bolus hypertonic saline, however, may prevent the microcirculatory changes seen in shock[1] and this treatment may be less effective in the clinical setting of acute pancreatitis since microcirculatory ischaemia may continue to evolve during the course of the illness[2,3]. In this context, it would be of some additional benefit (although perhaps ethically and practically difficult) to examine whether the benefits of hypertonic saline infusion were sustained beyond 72 hours.

Further, microcirculatory patency maintained by hypertonic saline provides a potential access route for therapies directed at modulation of pancreatic acinar injury. In this context, hypertonic saline may prove to be a useful adjunct in the current Manchester trial of high-dose multiple-antioxidant therapy in patients with predicted severe acute pancreatitis. The role of hypertonic saline in acute pancreatitis, whether used alone or in conjunction with other therapies, is worthy of further appraisal.

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Authors' reply

Sir

We thank Messrs. Virlos and Siriwardena for their interest in our paper. We agree that pancreatic microvascular changes are significant determinants of severity and exacerbate acinar injury[1]. This suggests a susceptibility of the pancreas to changes in its blood supply, and that a restitution of pancreatic microcirculation early in the course of the disease may attenuate acinar necrosis. Hypertonic saline, by reducing endothelial cell swelling[2], may ensure nutritive and therapeutic delivery to organs that would otherwise remain underperfused during local and systemic haemodynamic dysfunction. Therefore, its use as an adjuvant to ensure delivery of antioxidant therapy in pancreatitis is an intriguing and theoretically plausible suggestion. However, while some may advocate progression to a clinical trial, we would like to proffer a caveat. Although rare, osmotic demyelination (pontine myelinolysis) is a devastating complication of aggressive hypertonic therapy in hyponatraemia[3], which may occur in patients with pancreatitis. The risk of myelinolysis is increased in the presence of the hepatic failure and nutritional compromise that may accompany severe pancreatitis. Furthermore, hypertonic saline states may induce venous thrombosis[4]. Therefore, we believe that the implications of our findings with hypertonic infusion in pancreatitis need further elucidation prior to clinical trial.

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Postoperative ileus: a preventable event (*Br J Surg* 2000; 87: 1480–93)

Letter 1

Sir

We thank the authors for their brilliant update of knowledge on the pathophysiology and treatment of postoperative ileus. The article suggests that the use of the prokinetic agent cisapride is beneficial. We would like to bring to the attention of readers that the Medicines Control Agency (MCA) has suspended the product licences in the UK for all medicinal products containing cisapride from 28 July 2000. The decision has been made pending the outcome of the discussion on the benefits : risks ratio of Prepulsid currently taking place by the

European Committee for Proprietary Medicinal Products (CPMP). Once a decision is made by CPMP, the UK authorities will reassess the status of the product licence for cisapride.

Cisapride interacts with drugs metabolized by the cytochrome P4503A4 liver enzyme system[1]. By inhibiting its metabolism such interactions may lead to raised cisapride blood levels which may cause Q–T interval prolongation and ventricular arrhythmias. Recent experimental evidence suggests that therapeutic concentrations of cisapride have direct electrophysiological effects on the heart[2]. Serious cardiac arrhythmias, including ventricular tachycardia, ventricular fibrillation and torsades de pointes, and cases of sudden death have been reported in patients taking cisapride. Many of these patients were taking drugs suspected to increase cisapride blood levels by inhibiting its metabolism; others had a pre-existing cardiac condition which may have predisposed them to arrhythmias.

We hope this letter will make readers aware that cisapride is a drug that is suspended for use at present. We must await the MCA reassessment of the status of the product licence.

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Letter 2

Sir

This review may have given the impression that surgeons should use cisapride to reduce the duration of ileus following laparotomy and the authors quote randomized controlled trials which support this practice. However, cisapride is associated with prolongation of the Q–T interval, which may lead to fatal ventricular arrhythmias. Because of this rare, but life threatening complication, cisapride was withdrawn from the market earlier this year. Further details may be found at the websites of the Medicines Control Agency in the UK (www.open.gov.uk/mca) and the Food and Drug Administration in the USA (www.fda.gov/bbs/topics/answers/ans01007.html).

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Role of surgery in mild primary hyperparathyroidism in the elderly (*Br J Surg* 2000; 87: 1640–49)

Letter 1

Sir

The statistic quoted by the authors of a greater than 90 per cent success rate for neck exploration 'with very low morbidity and mortality' may not be universally valid. There is likely to be a mixed ability of participants in this branch of surgery. An analogous situation exists in at least one other subspecialty, giving rise to the question 'who should do thyroid surgery?'[1]. In the latter context, the recommendation is for increasing specialization[1]. This should apply with equal force to parathyroid surgery, given the implicit acknowledgement that the most useful adjunct to successful neck exploration is the experience of the surgeon[2], even rendering unnecessary the expedient of preoperative localization by imaging studies[3]. In highly vulnerable age groups such as the elderly, it should be the policy in all hospitals to channel all referrals for parathyroidectomy to surgeons with a declared commitment to this branch of surgery.

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2 Silverberg SJ, Bilezikian JP. Evaluation and management of primary hyperparathyroidism. *J Clin Endocrinol Metab* 1996; **81**: 2036–40.
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Letter 2

Sir

The first conclusion in this review is that no prospective randomized controlled trial comparing parathyroidectomy with conservative management for patients with mild or asymptomatic hyperparathyroidism has been published. I would make reference to the work of Silverberg *et al.*: 'A 10-year prospective study of primary hyperparathyroidism with or without parathyroid surgery'[1].

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1 Silverberg SJ, Shane E, Jacobs TP, Siris E, Bilezikian JP. A 10-year prospective study of primary hyperparathyroidism with or without parathyroid surgery. *N Engl J Med* 1999; **341**: 1249–55.

Essential Postgraduate Surgery

L. Fligelstone, A. H. Davies (eds)
215 × 138 mm Pp. 405. Illustrated 2001. Edinburgh. Churchill Livingstone
£24·95

This surgical textbook summarizes a high proportion of the knowledge needed for the Membership of the Royal College of Surgeons examination. The information would be of value to the senior house officer and registrar. It is up to date and is written by a variety of contributors, using many lists and some excellent algorithms. The chapters on orthopaedic, vascular, endocrine, upper gastrointestinal, pancreatic, biliary and breast surgery are particularly useful. This reviewer was, however, disappointed not to see more on intensive care, which is such an important part of the College examination course. Little is written on, for example, renal or liver failure. Nevertheless, this volume is useful as a revision text for junior surgeons approaching the membership examination.

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Practical Management of Oesophageal Disease

A. Adam, R. C. Mason, W. J. Owen (eds)
257 × 191 mm. Pp. 214 Illustrated. 2000 Oxford: Isis Medical Media. £69·95

This book covers all the relevant topics of oesophagology – motility disorders, oesophageal cancer, oesophagotracheal fistula, perforation and 'miscellaneous'; it includes a separate chapter on clinical history taking and on the place of the oesophageal laboratory. A word of warning about the influence of expertise on the interpretation of the results obtained with manometry/24 h pH monitoring and on the relationship between surgical experience and outcome of treatment is lacking. For gastro-oesophageal reflux disease, the indications for surgery and the surgical options are discussed. The lack of comparative studies in the literature produces a tendency to dogmatism, such as 'recurrent reflux disease is more common after partial fundoplication than after Nissen'. This, and other similar statements, are largely opinion, often lacking confirmation from clinical studies. The decompensated oesophagus, sometimes surprisingly asymptomatic and severely compromising both dilatation and surgery, is a well-recognized and problematic condition that should have been discussed by the authors in the section on achalasia. They have included a chapter on quality of life in the section on oesophageal cancer. Quality of life studies were introduced in the 1980s and held major promise in assisting difficult clinical decisions. So far their contribution has been disappointing. Moreover, the potential of quality of life analysis is not confined to malignant disease but plays an equally important role in the treatment of benign oesophageal disease. The book is both practical and useful, but it does not give guidelines about who should treat which patient and, in particular, does not tell the reader when to refrain from surgical intervention and to consider referral to an expert unit. This is of specific relevance to the surgical trainee and the newly qualified physician with an interest in oesophageal disorders.

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Applied Basic Science for Basic Surgical Training

A. T. Raftery (ed)
245 × 188 mm. Pp 607 Illustrated 2000. Edinburgh Churchill Livingstone
£47 95.

In the preface to this text the Editor stresses that the book is intended to fill the gap between curtailed undergraduate medical education and Membership of the Royal College of Surgeons examinations. Comparing the size of this volume with those on the groaning bookshelves of most surgical trainees demonstrates this book's major failing; many of the sections contain insufficient information to pass surgical examinations. I have discussed the contents with several of the trainees I have worked with in relation to their examination experiences and in no case did they feel that there was sufficient information in this book to have satisfied the examiners that they encountered. That should not, however, detract from the text as it stands. It is clearly written and well illustrated. It would certainly form a useful basis for revision and would act as a guide to further areas of study. To try and encompass the whole of surgical education in one text is obviously a very tall order but this volume does go some way towards it. It would be of interest to undergraduates, postgraduates studying for surgical examinations and, indeed, ancillary staff working with surgeons.

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Scientific Surgery

The *British Journal of Surgery* is committed to practice of surgery based on scientific evidence. Each month we will publish a list of randomized trials and meta-analyses collated from English-language publications. A collection of all these papers will be available in the Scientific Surgery Archive which will be held on the *British Journal of Surgery* website together with links to free Medline sites where the full papers can be accessed (see below for details). If you have published a recent randomized trial which has not been featured in Scientific Surgery, the Editors would be pleased to receive a reprint and consider its inclusion.

Skoropad VY, Berdov BA, Mardynski YS, Titova LN. A prospective randomized trial of preoperative and intraoperative radiotherapy *versus* surgery alone in resectable gastric cancer. *Eur J Surg Oncol* 2000; **26**: 773–9.
There was no overall survival advantage in this trial including 78 patients (50 per cent at 5 years), however, survival was significantly prolonged in a subgroup of patients with advanced disease.

Schweizer J, Kirch W, Koch R, Elix H, Hellner G, Forkman L *et al.* Short- and long-term results after thrombolytic treatment of deep venous thrombosis. *J Am Coll Cardiol* 2000; **4**: 1336–43.
Some 250 patients with acute deep venous thrombosis were randomized into five groups – one control and four different thrombolytic regimens. Systemic thrombolysis improved the clinical outcome but significantly increased the risk of bleeding and pulmonary emboli.

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Some 141 trials including nearly 10 000 patients were analysed. Mortality was decreased by about one third, complications such as deep venous thrombosis, pulmonary embolism, pneumonia and transfusion requirement were also reduced.

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Forty patients were randomized. Operative and postoperative clinical outcomes were similar but patients who had hypnosedation reported significantly less postoperative pain

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The trial included 36 patients studied for 24 months. Photodynamic therapy significantly reduced the area of Barrett's oesophagus (median decrease 30 per cent) and the rate of dysplasia on biopsy.

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There was no difference in 5-year recurrence-free survival (64 per cent doxorubicin regimen *versus* 78 per cent fluorouracil regimen) in this study including 124 women

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Bupivacaine given preoperatively, intraoperatively and postoperatively significantly improved postoperative pain scores for the first 10 days in this study of 70 hernia repairs.

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Some 53 patients were randomized. After 2 years, two of nine quality of life domains were significantly better in patients randomized to surgery

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Some 222 women were randomized into one of four groups, placebo, or one of three different doses of this antidepressant drug. Active treatment reduced the rate of flushing by 37 to 61 per cent at the expense of symptoms such as dry mouth and occasional nausea

The *British Journal of Surgery* website can be found at *www.bjs.co.uk*. In addition to details of current and previous articles featured in Scientific Surgery, the website contains details of the Editorial Team and Board, instructions to prospective authors, links to other sites (such as The Cochrane Library) and forthcoming surgical events. The Editors welcome comments and suggestions about the website, either in writing or through the website address.

Vascular Surgical Society of Great Britain and Ireland

The following abstracts are from the papers presented at the Millennium Annual Meeting of the Vascular Surgical Society of Great Britain and Ireland, held in London, UK, from 30 November to 1 December 2000. The President of the Society, Professor R. M. Greenhalgh, was in the Chair.

Distal arterial reconstruction in Scotland 1989–1998

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Methods: A retrospective analysis of national hospital discharge data (Scottish Morbidity Record 1) from 1989 to 1998 was undertaken.

Results: The population of Scotland has remained constant at 5·1 million. A total of 975 distal arterial grafts were performed in 10 years. The overall rate of distal reconstruction increased from 0·9 per 100 000 population in 1989, peaked at 2·6 per 100 000 in 1994, and has since declined steadily to 1·8 per 100 000 in 1998 (*Table*). There were huge interregional variations in the rate of reconstruction, with up to a 17-fold variation in annual rates between the 12 mainland health boards. The variations in distal reconstruction between the health boards were not reflected in reduced amputation rates, nor was the decline in distal reconstruction easily explained by increased non-femoral angioplasty.

Conclusion: Rates of distal arterial reconstruction in Scotland fall well below those of comparable European countries. It is likely that insufficient distal operations are undertaken to impact on amputation rates. The authors recommend an increased provision of specialist vascular surgical expertise in Scotland.

Association between intraplaque haemorrhage in the carotid atherosclerotic lesion, the degree of internal carotid artery stenosis and timing of ischaemic neurological events

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Background: Expansion of carotid atherosclerotic plaques as a result of intraplaque haemorrhage has been implicated in the development of ischaemic neurological events. The relationship between the quantity of haemorrhage in the dominant atherosclerotic lesion, the degree of internal carotid artery (ICA) stenosis and the chronology of patients' symptoms was examined.

Methods: Consecutive patients undergoing carotid endarterectomy were included. The nature and timing of symptoms were recorded. Aortic arch injection digital subtraction angiography was performed before operation. Carotid endarterectomy specimens were serially sectioned and examined histologically. The amount of intraplaque haemorrhage was measured with digital image analysis. The influence of timing of symptoms on the quantity of intraplaque haemorrhage was compared with Kaplan–Meier analysis. Correlation between degree of ICA stenosis and quantity of intraplaque haemorrhage was assessed by means of regression analysis.

Results: Seventy-four patients (20 asymptomatic, 54 symptomatic) were included. The median latency of symptoms was 28 (1–600) days. Intraplaque haemorrhage was common: 54 (73 per cent) of 74 patients. Mean(s.e.m.) cumulative symptom-free survival before operation for patients with no intraplaque haemorrhage was 0·71(0·11), compared with 0·58(0·11) in those exhibiting haemorrhage in less than 50 per cent of the plaque area, and 0·20(0·07) in lesions with over 50 per cent (P = 0·002). A close correlation was observed between the degree of ICA stenosis and haemorrhagic content of the dominant atherosclerotic lesion (r^2 = 0·433, P < 0·001).

Conclusion: These results confirm the association between intraplaque haemorrhage and the degree of ICA stenosis. They further demonstrate an association between the size of haemorrhage and timing of neurological events, suggesting a causative role for intraplaque haemorrhage in the development of ischaemic neurological events.

Table Distal arterial reconstruction in Scotland 1989–1998, R. J. Holdsworth and H. M. Paterson

	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998
Total grafts	47	57	102	126	102	133	105	118	94	91
Rate per 100 000 per year	0·92	1·18	2·00	2·47	1·97	2·59	2·04	2·30	1·83	1·75
No. of non-femoral angioplasties	245	173	124	158	180	139	226	193	186	237
No. of amputations	823	834	813	836	944	852	922	815	849	775

Randomized trial of vein *versus* dacron patching during carotid endarterectomy

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Background: A recent overview has indicated that, while routine patching is safer than primary closure following carotid endarterectomy (CEA), there is no systematic evidence that patch type influences outcome. Most surgeons perceive that prosthetic patches are more thrombogenic than vein patches. This study tested the hypothesis that it is the patient who is prothrombotic rather than the nature of the patch.
Methods: Some 274 patients undergoing 276 CEAs were randomized to either dacron (Du Pont, Stevenage, UK) patch closure ($n = 137$) or vein patch closure ($n = 139$). All patients with an accessible cranial window were monitored for 3 h after operation using transcranial Doppler (TCD) ultrasonography. The number and rate of embolizations were quantified, together with the requirement for selective dextran therapy to control high rates of postoperative embolization. All patients were assessed after operation and again at 30 days by a neurologist, and all underwent duplex imaging at 30 days.
Results: The 30-day death or any stroke rate was 2·2 per cent for dacron-patched patients and 3·6 per cent for vein-patched patients ($P = 0{\cdot}72$). Dacron-patched patients had a higher incidence of postoperative emboli (median 5 (interquartile range 0–10·5)), compared with a median of 3 (interquartile range 1–17) for vein ($P = 0{\cdot}028$). However, the incidence of detecting more than 50 emboli was virtually identical and patch type had no effect on the incidence of sustained high-rate embolization requiring dextran therapy (5·3 per cent for dacron *versus* 3·7 per cent for vein). No patient had a carotid thrombosis at 30 days.
Conclusion: Sustained high-rate embolization, previously shown to be highly predictive of progression to carotid thrombosis, appears to be patient dependent rather than related to patch type.

Comparison of primary closure with dacron patch angioplasty in early and late restenosis after carotid endarterectomy

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Background: The primary closure of carotid arteriotomy has a high incidence of intraoperative residual stenosis following carotid endarterectomy.
Methods: Completion angiograms in a consecutive series of 197 patients undergoing carotid endarterectomy were reviewed. All operations were performed under general anaesthesia with routine shunt insertion and middle cerebral artery transcranial Doppler monitoring. The first 117 patients had primary closure of the arteriotomy and the last 80 all had patch closure. An independent radiologist, who was unaware of the procedure performed, randomly assessed the intraoperative angiograms. All patients have been followed by 3-monthly duplex screening for 1 year. Results were assessed with the χ^2 test.
Results: The stroke and death rate of 7 per cent in the primary closure group was significantly higher than the 1 per cent stroke and death rate in the patched group ($P < 0{\cdot}05$). Perioperative angiograms scored 0–20 per cent residual stenosis in 75 per cent of the primary closures, compared with 89 per cent in the patched group ($P < 0{\cdot}05$). Some 25 per cent of the primary closures were considered unsatisfactory, compared with 11 per cent of the patched closures. Restenosis greater than 50 per cent at 1 year was significantly higher in the primary closure group (33 *versus* 19 per cent; $P < 0{\cdot}05$).
Conclusion: Patch closure results in a better technical result than primary closure, as judged by radiological appearance, and reduces the overall stroke and death rate. Restenosis is significantly lower at 1 year.

Vein interposition grafting is a safe and durable method of repairing carotid arteries that are not suitable for standard endarterectomy

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Background: Standard carotid endarterectomy (CEA) and patch angioplasty is an effective method of reducing the risk of stroke associated with carotid atherosclerosis. If the posterior wall of the carotid artery becomes excessively thinned following endarterectomy, or the vessel is exceptionally tortuous, this standard approach to repair is not always appropriate. A different approach may also be necessary when an existing carotid patch becomes infected. In a number of these cases the authors have utilized a vein interposition graft to repair the vessel. This study examined the safety and durability of this procedure.
Methods: During the 5-year study, a standard operative protocol was followed including routine shunting and perioperative monitoring. All data were collected prospectively. Long saphenous vein harvested from the groin was used as a graft. Patients were entered into a regular duplex graft surveillance programme.
Results: Forty patients had a vein graft inserted (4·3 per cent of all CEAs performed). Age, sex and presentation were not significantly different from those in patients undergoing routine CEA. There were no vein graft ruptures or deaths. The 30-day any stroke or death rate was 5 per cent. The operation was not significantly lengthened relative to standard CEA. The median length of follow-up was 29 (range 4–48) months. Five patients required subsequent angioplasty to treat stenosis in the graft of more than 70 per cent, this is significantly higher than with standard CEA ($P < 0{\cdot}001$). One patient developed an asymptomatic occlusion. At 1-year

follow-up, 11 per cent of patients had a stenosis greater than 70 per cent, and at 2 years this was 6 per cent.

Conclusion: Interposition vein grafts can be used safely to repair the carotid artery when the standard technique does not appear appropriate. There is an increased rate of restenosis in this group and patients therefore require regular duplex surveillance of the graft.

Assessment of degree of internal carotid artery stenosis based on duplex velocity measurements using an artificial neural network

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Background: Duplex imaging is increasingly used as a stand-alone investigation before carotid endarterectomy. There is concern regarding the wide variation in diagnostic methods of grading internal carotid artery (ICA) stenosis using duplex velocity criteria. The aim of the study was to design an artificial neural network (ANN) that is able to provide a measure of the degree of ICA stenosis based on the four most commonly used duplex velocity profiles.

Methods: One hundred and four consecutive patients who were admitted for assessment of carotid occlusive disease were included. All patients underwent arch injection digital subtraction angiography and carotid duplex ultrasonography. Peak systolic velocity (PSV) and end-diastolic velocity (EDV) in the ICA and common carotid artery (CCA) were measured. The degree of angiographic stenosis was measured by two blinded investigators. A three-layered perceptron ANN was constructed using the NeuroSolutions™ version 1 software program (NeuroDimension, Gainesville, FL, USA). The accuracy of the model in predicting the degree of ICA stenosis was expressed as the mean squared error (MSE) of the actual degree of angiographic stenosis. The performance of the neural network model was compared with that of the linear regression model at predicting the degree of ICA stenosis and classifying a degree of ICA stenosis greater than 50 per cent.

Results: One hundred and sixty-eight carotid bifurcations were available for analysis. The MSE of the ANN at predicting the degree of ICA stenosis was 0·096 (overall accuracy of 84 per cent), which was superior to a linear regression model (MSE 0·132; overall accuracy 73 per cent) ($P < 0{\cdot}001$). Both models were equally accurate at identifying a degree of ICA stenosis greater than 50 per cent (ANN accuracy 0·91 *versus* regression model accuracy 0·89; $P = 0{\cdot}09$).

Conclusion: Neural network algorithms are able to predict the degree of ICA stenosis with reasonable accuracy and outperform linear regression analysis on the basis of a limited set of duplex velocity measurements. With further refinement, ANN models could replace duplex criteria in assessment of the degree of ICA stenosis.

Jugular venous neurone-specific enolase and s-100 levels after carotid endarterectomy under local or general anaesthesia

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Background: Previous studies using near infrared spectroscopy have indicated that carotid endarterectomy (CEA) performed under local anaesthesia (LA) preserves cerebral cytochrome oxidase and autoregulation compared with surgery under general anaesthesia (GA). The hypothesis that LA offers a degree of protection against ischaemic cerebral injury has thus been investigated by measuring ipsilateral jugular venous neurone-specific enolase (NSE; a glycolytic enzyme released from injured neurones) and s-100 (a protein released from glial cells) during and after CEA.

Methods: Sixteen patients with symptomatic 70–99 per cent carotid stenosis were randomized (with ethics committee approval) to CEA with either LA ($n = 7$; mean stump pressure 48·5 (range 37–80) mmHg; none of seven shunted) or GA ($n = 9$; mean stump pressure 49·1 mmHg; five of nine shunted). Jugular venous samples were assayed for NSE and s-100 concentration (immunoluminometric assay) before carotid clamping, 5 min before and 5 min, 2, 4, 6, 8, 12 and 24 h after clamp release.

Results: There were no neurological complications. Median (range) levels of s-100 were low and did not increase from baseline levels (GA 0·10 (0·08–0·11) $\mu g\,l^{-1}$, LA 0·13 (0·12–0·17) $\mu g\,l^{-1}$) in either group . Preclamp NSE levels were similar in both groups (LA 17·6 (15·2–20·7) $\mu g\,l^{-1}$ *versus* GA 21·5 (11·3–26·2) $\mu g\,l^{-1}$; $P = 0{\cdot}37$). Peak levels occurred at 2 h and were significantly higher in patients having GA (48·2 (31·4–61·3) *versus* 25·5 (16·6–27·8) $\mu g\,l^{-1}$; $P = 0{\cdot}05$, Mann–Whitney *U* test). Furthermore, the increase from baseline in patients having GA was also significant ($P = 0{\cdot}04$) and NSE levels were higher at all time points up to 12 h, returning to baseline at 24 h.

Conclusion: These results suggest that CEA performed under LA is associated with reduced cerebral ischaemic injury compared with GA, and are consistent with niroscopic data indicating improved cerebral oxygenation in these patients. Furthermore, NSE would seem to be a more sensitive marker of cerebral injury than s-100.

A carotid POSSUM model for predicting death

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Background: Risk adjustment to allow for differences in case mix aids comparative audit of carotid endarterectomy (CEA). The aim of this study was to test the predictive accuracy of P-POSSUM (Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity

– Portsmouth predictor equation for mortality) and V-POSSUM (P-POSSUM-based model for vascular surgery) and to develop a procedure-specific model for CEA.

Methods: A total of 709 CEAs performed in two vascular units from 1992 to 2000 were analysed. The physiological and the operative severity scores were calculated; the outcome used was 30-day mortality. Predicted mortality was calculated using P-POSSUM, V-POSSUM and V-POSSUM (physiology only = PS) equations. The observed and the predicted mortality were compared. The new model was developed on a set of 350 CEAs and validated on 359 CEAs. The data sets of the two units were combined and split into two by the procedure date order. The predictive accuracy of the model was analysed with the χ^2 test.

Results:

	Observed deaths	Predicted deaths	χ^2	*P*
P-POSSUM	11	31	15·8	0·003
V-POSSUM	11	37	22·9	<0·001
V-POSSUM (PS)	11	48	33·9	<0·001

P-POSSUM and V-POSSUM models showed lack of fit in predicting death.

	Observed deaths	Predicted deaths	χ^2	*P*
Carotid model	4	6	2·0	0·728
Carotid model (PS)	4	8	3·8	0·440

There was no evidence of any lack of fit in the new model.

Conclusion: P-POSSUM and V-POSSUM overpredict mortality and are unsuitable for the comparative audit of CEA. Procedure-specific models based on P-POSSUM can accurately predict death.

Endovascular intervention compared with carotid endarterectomy

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Background: Endovascular intervention has only recently been used for the treatment of carotid disease. The 30-day outcome of 226 endovascular carotid interventions for atherosclerosis performed since August 1993 is presented.

Methods: All patients were symptomatic apart from four (2 per cent) who underwent intervention before coronary artery bypass. The last presenting symptom was transient ischaemic attack (TIA) (40 per cent), amaurosis fugax (31 per cent), retinal artery occlusion (3 per cent) and stroke (24 per cent). A moderate stenosis (50–69 per cent; North American Symptomatic Carotid Endarterectomy Trial technique) was present in 24 patients (11 per cent), a severe stenosis (70–95 per cent) in 144 (64 per cent), and a preocclusive stenosis (more than 95 per cent) in 58 (26 per cent). The contralateral internal carotid artery was significantly diseased (greater than 70 per cent) or occluded in 65 patients (29 per cent). All patients were pretreated with aspirin; 5000 units heparin and 1·2 mg atropine were given during the procedure. Initially, stents were reserved for treating residual stenosis after angioplasty (16 of 108 procedures). Later, a change was made to primary stenting (116 procedures). A femoral approach was used for all patients.

Results: At 30 days there were four deaths (2 per cent) and eight disabling strokes (4 per cent) (death and disabling stroke rate 5 per cent; death and all-strokes rate 8 per cent). For angioplasty and selective stenting the death and disabling stroke rate and the death and all-strokes rate were 6 and 9 per cent respectively, compared with 5 and 8 per cent for primary stenting (*P* not significant). However, there was a significant difference between the incidence of all adverse events (31 *versus* 11 per cent) as a result of fewer TIAs associated with primary stenting. During the same interval, 300 carotid endarterectomies (similar indications and severity of disease) were performed. There were six deaths (2 per cent) and eight disabling strokes (3 per cent) (death and disabling stroke rate 5 per cent; death and all-strokes rate 6 per cent). The complications of both endovascular intervention and conventional endarterectomy seem to be improving with time.

Conclusion: These data confirm the feasibility of endovascular carotid intervention and highlight the need for a large randomized trial comparing it with conventional surgery. The benefit of stents and cerebral protection systems also requires further investigation.

Interleukin 6 and the prognosis of abdominal aortic aneurysms

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Background: Abdominal aortic aneurysm (AAA) is a familial disorder, inflammation being an important pathophysiological feature. Increased plasma concentrations of the inflammatory cytokine interleukin (IL) 6 have been associated with AAA and early aortic dilatation. This study was designed to test the hypothesis that high concentrations of plasma IL-6 and/or IL-6 genotype predict rapid AAA growth.

Methods: Genomic DNA from 466 patients, kept under ultrasonographic surveillance for small AAAs, was analysed for a G to C polymorphism at position −174 of the IL-6 promoter. Baseline plasma IL-6 concentration was measured by enzyme-linked immunosorbent assay and AAA growth rates were calculated by linear regression.

Results: The median concentration of plasma IL-6 was 4·9 (range 0–604) pg ml^{-1}. IL-6 concentration was not associated with aneurysm growth rate. The frequency of the C allele was 0·40, similar to that in the healthy population. Patients of GG genotype had a lower plasma concentration of IL-6 than patients of either GC or CC genotype (median 1·9, 4·8 and

15·6 pg ml^{-1} respectively; P = 0·047, Kruskal–Wallis test). The AAA growth rate for patients of GG, GC and CC genotypes was 0·38, 0·36 and 0·36 cm per year respectively (P = 0·37). Mortality was lower for patients of GG genotype than for those with GC or CC genotype: hazard ratio 0·51 (95 per cent confidence interval (c.i.) 0·25–1·00), P = 0·05; and 0·32 (95 per cent c.i. 0·12–0·93), P = 0·036, for all-cause and cardiovascular mortality respectively.

Conclusion: Genetic polymorphism is associated with clinical events in patients with an AAA. The G to C IL-6 polymorphism at position −174 predicts future cardiovascular mortality. Neither plasma IL-6 concentration nor IL-6 genotype predicts AAA growth.

Ischaemic preconditioning before lower limb ischaemia–reperfusion protects against acute lung injury

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Background: Ischaemic preconditioning (IPC) of skeletal muscle, by exposing it to repeated brief periods of ischaemia and reperfusion (I-R) before a subsequent longer ischaemic period, protects against local damage on reperfusion. In a large animal model of hindlimb I-R it was hypothesized that hindlimb IPC would attenuate the systemic inflammatory response syndrome and prevent acute lung injury associated with limb reperfusion injury.

Methods: Anaesthetized ventilated swine (six per group) were used throughout. After midline laparotomy, animals were randomized to the following three groups: bilateral external iliac artery occlusion for 120 min, followed by reperfusion for 180 min (I-R group); IPC (three cycles of 5 min ischaemia, then 5 min reperfusion of both external iliac arteries) followed by bilateral external iliac artery occlusion for 120 min and reperfusion for 180 min (I-R + IPC group); or laparotomy alone (control group). Acute lung injury was assessed by invasive pulmonary artery pressure (PAP) measurement, arterial to alveolar (A-a) oxygen gradient, lung tissue wet : dry weight ratio, and lung myeloperoxidase (MPO) concentration.

Results:

	Control	I-R	I-R + IPC
PAP (mmHg)*	27·9(1·9)	42·0(4·6)§	31·0(1·8)¶
Wet : dry ratio†	5·57 (4·54–7·37)	10·1 (7·7–12·7)‡	6·6 (5·7–7·1)**
MPO (units g^{-1})†	7·5 (0·9–8·6)	33·8 (15·7–52·7)§	19·9 (16·8–20·7)**
A-a gradient*	283·7(70·7)	476·6(76·8)§	359·2(43·5)**

Values are *mean(s.e.m.) (compared with Student's t test) or †median (interquartile range) (compared with Mann–Whitney U test). ‡P < 0·05, §P < 0·01 *versus* control group; ¶P < 0·01, **P < 0·05 *versus* I-R

Conclusion: Lower limb I-R induces systemic inflammation and acutely impairs oxygen transport associated with lung neutrophil sequestration. IPC attenuates acute pulmonary hypertension, impairment of oxygen transport, oedema and leucosequestration in planned lower limb I-R.

An endothelin type A receptor antagonist inhibits neointimal hyperplasia and increases luminal area in porcine vein grafts

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Background: Neointimal hyperplasia is responsible for the majority of cases of vein graft failure. To date, no pharmacological intervention has proved successful in preventing this process in humans. Endothelin (ET) 1 is a potent vasoconstrictor and promotes the proliferation of vascular smooth muscle cells *in vitro*. The authors have shown previously that porcine vein grafts contain high levels of ET-1 and ET type A (ET$_A$) receptor subtypes. The aim was to investigate the effect of an ET$_A$ receptor antagonist, BSF 302146, on luminal area and graft wall dimensions in a porcine model of arteriovenous bypass grafting.

Methods: Bilateral saphenous vein–carotid artery interposition grafting was performed in two groups of Large White pigs (26–32 kg; n = 5 per group). BSF 302146 (10 mg kg^{-1} day^{-1}) was administered orally to animals in group 1; group 2 animals acted as controls. After 4 weeks the grafts were explanted and pressure-fixed *ex vivo*. Histological sections were obtained and graft dimensions assessed by means of computer-aided planimetry.

Results: BSF 302146 significantly reduced both neointimal hyperplasia and medial thickening, and increased luminal area by 77 per cent.

	Control	BSF 302146
Luminal area (mm^2)	37·6(2·2)	66·7(3·9)*
Neointimal thickness (mm)	0·15(0·009)	0·11(0·004)*
Medial thickness (mm)	0·32(0·011)	0·25(0·014)

Values are mean(s.e.m.); n = 10. *P < 0·001 (paired t test)

Conclusion: The ET$_A$ receptor antagonist BSF 302146 inhibits neointimal hyperplasia and increases luminal area in a porcine model of saphenous vein bypass grafting.

Cyclo-oxygenase 1 and 2 expression is augmented in symptomatic carotid plaques

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Background: Macrophage accumulation and increased metalloproteinase levels within carotid plaques are associated with plaque instability. Production of the latter by macrophages and vascular smooth muscle cells (VSMCs) is promoted by prostaglandins synthesized following the action of cyclo-oxygenase (COX) on arachidonic acid.

Methods: Expression of the isoenzymes COX-1 and COX-2 was assessed in carotid plaques removed from 12 asymptomatic patients and 11 patients who had had a neurological event within 30 days of carotid endarterectomy. Patients were matched for age, sex, risk factors and degree of stenosis. For each plaque, paraffin sections obtained at 3-mm intervals throughout its length were stained with goat antihuman antibodies to COX-1 and COX-2. The percentage of the area that stained positively was determined within the cap, shoulder regions and sclerotic component of the plaques (computerized planimetry).

Results: The median (interquartile range) percentage area staining for COX-1 (symptomatic *versus* asymptomatic) was: cap 8·37 (4·38–13·65) *versus* 1·07 (0·31–4·51) per cent, $P<0\cdot0006$; shoulder 11·76 (3·02–29·48) *versus* 1·41 (0·73–2·70) per cent, $P<0\cdot0026$; sclerotic component 0·08 (0·02–0·54) *versus* 0·06 (0·04–0·24) per cent, $P<0\cdot4$. Values for COX-2 were: cap 9·62 (4·87–12·50) *versus* 0·27 (0·02–2·41) per cent, $P<0\cdot0001$; shoulder 11·45 (2·34–24·16) *versus* 0·44 (0·02–2·97) per cent, $P<0\cdot0038$; sclerotic component 1·36 (0·24–2·61) *versus* 0·06 (0·02–0·49) per cent, $P<0\cdot0081$. Further, COX-2 expression was greater than COX-1 staining in the sclerotic component of the plaques ($P<0\cdot05$, Mann–Whitney U test).

Conclusion: Plaques that had recently become symptomatic exhibited increased COX-1 and COX-2 expression, particularly in the cap and shoulder regions. Such changes would increase macrophage and VSMC metalloproteinase production (collagenolysis) and reduce collagen synthesis by VSMCs. Such events are likely to promote plaque instability or rupture. These findings suggest that COX-1 and COX-2 inhibitors might have a therapeutic role in the prevention of further neurological events.

Angiogenesis in carotid atherosclerosis: the association with morphological features of plaque instability

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Background: Intimal angiogenesis is a recognized feature of the atherosclerotic process. It has been described in the context of unstable coronary atherosclerotic lesions. The aims of this study were to assess the association between angiogenesis in atherosclerotic plaques and microscopic features of plaque instability, in particular intraplaque haemorrhage.

Methods: Consecutive patients undergoing carotid endarterectomy for carotid stenosis were included in the study. Endarterectomy specimens were examined and divided into their constituent atherosclerotic lesions. Histological sections were prepared and stained with haematoxylin and eosin, and immunohistochemically with an endothelial cell marker (CD34). Each lesion was classified according to the American Heart Association classification of atherosclerotic lesions. The size of plaque haemorrhage was measured in transverse histological sections using computerized image analysis. Haemorrhagic lesions were classified according to the size of haemorrhagic area (under 50 per cent of section area; over 50 per cent of section area). Microvessel counts were performed in CD34-stained sections at × 400 magnification and were verified with computerized image analysis. The Kruskal–Wallis test was used to study the differences in microvessel count in different atherosclerotic plaque types.

Results: A total of 239 atherosclerotic lesions from 73 patients was available for analysis, of which 73 were early lesions, 74 were raised fibroatheromas and 92 were unstable atherosclerotic plaques. One hundred and fifty lesions were not haemorrhagic; 89 exhibited intraplaque haemorrhage, of which 28 involved less than 50 per cent of the plaque section area. In 61 lesions the haemorrhage area was over 50 per cent of the section area. There were higher microvessel counts in plaques containing more than 50 per cent haemorrhage (median 277 (range 43–467)) compared with those containing less than 50 per cent (172 (57–372)) and non-haemorrhagic plaques (81 (7–389)) ($P<0\cdot0001$). Higher microvessel counts were observed in unstable atherosclerotic lesions (median 252 (range 43–467)), compared with stable fibroatheromas (106 (14–302)) and early atherosclerotic lesions (55 (7–237)) ($P<0\cdot0001$).

Conclusion: There are strong associations between plaque vascularity and presence and size of haemorrhage within atherosclerotic lesions, as well as features of plaque instability. This finding highlights the likely significance of these new blood vessels in the development of plaque instability and subsequent risk of stroke.

Randomized controlled trial of acute normovolaemic haemodilution in aortic aneurysm repair

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Background: Previous studies have suggested that acute normovolaemic haemodilution (ANH) reduces the need for heterologous blood transfusion in abdominal aortic aneurysm (AAA) surgery and may thus improve postoperative outcome by reducing the systemic inflammatory response. Controlled studies are lacking. The aim of this randomized controlled trial was to evaluate the effects of ANH on the systemic inflammatory response, clinical outcome and use of bank blood after AAA repair.

Methods: Patients undergoing elective AAA repair were randomized to ANH ($n=16$) or control ($n=18$) groups. Intraoperative cell salvage and heterologous blood were used in both groups according to predetermined transfusion triggers. Inflammatory markers in serum and urine were measured to assess the acute-phase response. Clinical outcome was determined using mortality, morbidity and the incidence of the systemic inflammatory response syndrome (SIRS).

Results: There was no difference between the ANH and control group in serial measurements of median (range) white cell count (maximum at 2 days after operation: 11·9 (7·7–21·4) *versus* 10·3 (7·8–20·6) × $10^9\,\mathrm{l}^{-1}$; $P = 0·25$), serum C-reactive protein level (maximum at 3 days: 150 (1–274) *versus* 169 (7–238) mg ml^{-1}; $P = 0·76$), interleukin 6 level (maximum at 6 h: 142 (32–793) *versus* 105 (29–509) pg ml^{-1}; $P = 0·89$), total antioxidant capacity (lowest at 1 h: 0·83 (0·67–1·22) *versus* 0·83 (0·68–1·23) mmol l^{-1}; $P = 0·45$) or urinary albumin/creatinine ratio (maximum at 30 min after clamp release: 41 (2–923) *versus* 124 (4–376) mg ml^{-1}; $P = 0·10$). SIRS was observed in ten of 16 patients having ANH and in 11 of 18 control patients ($P = 0·99$). There was no significant difference in mortality and morbidity between the groups. Similarly, there was no difference in median (range) blood loss (ANH 1800 (400–12 000) ml *versus* control 1600 (500–7500) ml; $P = 0·55$), use of cell salvage (600 (0–4740) *versus* 520 (0–2420) ml; $P = 0·60$) or heterologous blood transfusion (2 (0–32) *versus* 2 (0–9) units; $P = 0·68$).

Conclusion: In the setting of a randomized controlled trial ANH added no additional benefit, when used in combination with cell salvage, in reducing the requirements for heterologous blood transfusion, and made no impact on systemic inflammatory response and clinical outcome after AAA repair.

Aneurysm-related mortality during late follow-up after endovascular aneurysm repair of infrarenal aorta

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Background: Aneurysm-related mortality (ARM) accounts for around 1·5 per cent of all deaths following open aneurysm repair. The incidence of ARM following endovascular aneurysm repair (EVAR) is unknown. The aim was to examine all causes of death, including ARM, during late follow-up after EVAR. ARM was defined as death resulting directly from rupture of the repaired aneurysm or another complication of the aneurysm, more than 30 days after repair, or death within 30 days of a secondary intervention undertaken solely to rectify a complication of repair.

Methods: Preoperative and follow-up data on 2194 patients from 88 European centres were collected prospectively on to a database. Survival up to 48 months after EVAR was analysed by means of Kaplan–Meier survival analysis. The causes of death during this period were noted.

Results: There were 161 deaths between 1 and 48 months after EVAR. The cumulative rate of secondary intervention for this cohort at 4 years was 33 per cent. The causes of death were: cardiac 28·6 per cent, malignancy 18·6 per cent, cerebrovascular 6·8 per cent, respiratory 3·1 per cent, renal 1·8 per cent, other 22·3 per cent and ARM 11·8 per cent. There were 19 deaths from aneurysm-related causes. Nine patients died following proven rupture of the aneurysm, three died from presumed rupture of the aneurysm and a further seven died following late conversion (three patients), graft sepsis (two) and secondary intervention (two). Sudden death of uncertain cause occurred in ten patients in whom rupture of AAA was a possibility.

Conclusion: Non-aneurysm-related causes of death were comparable to those in published reports of survival after open repair. However, the proportion of aneurysm-related deaths (11·8 per cent) was appreciably higher than that reported after open repair. These results may reflect the learning curve experience of the teams involved in the study, but continued caution is advisable regarding expectations of outcome following EVAR.

Autologous or homologous transfusion in aortic surgery: randomized trial

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Background: Aortic surgery often requires blood transfusion, which may cause complications and postoperative infection. Autologous transfusion was evaluated in a multicentre clinical trial.

Methods: Some 145 patients undergoing elective aortic surgery in eight hospitals were randomized to either 'homologous' or 'autologous' transfusion, a combination of acute normovolaemic haemodilution (ANH) and intraoperative cell salvage. Homologous blood was administered when the haemoglobin concentration fell below 8 g dl^{-1}.

Results: Median (interquartile range (i.q.r.)) blood loss was 668 (400–862) ml or 17 (10–24) per cent of blood volume in aortobifemoral bypass, and 1120 (765–1700) ml or 24 (17–36) per cent in aneurysm repair ($P < 0·001$). Autologous transfusion reduced homologous blood requirements from a median (i.q.r.) of 2 (0–4) units to 0 (0–2) units ($P = 0·008$). Independent predictors of blood transfusion were homologous transfusion strategy (odds ratio (OR) 2·3 (95 per cent confidence interval 1·1–5·0); $P = 0·03$), low preoperative haemoglobin concentration (OR 3·7 (1·7–8·2); $P < 0·001$), prolonged surgery (OR 2·1 (1·0–4·8); $P = 0·05$) and blood loss (OR 3·0 (1·4–6·5); $P = 0·007$). Patients with a preoperative haemoglobin concentration greater than 13·5 g dl^{-1} and who lost less than 20 per cent of their blood volume rarely required transfusion. There was no significant difference between the groups in terms of morbidity, mortality and postoperative hospital stay.

Conclusion: Autologous transfusion reduced the need for homologous blood in aortic surgery, but was useful only in patients with low haemoglobin levels or when blood loss exceeded 20 per cent of the blood volume. ANH alone is indicated for patients undergoing aortobifemoral bypass and in those with a higher haemoglobin level and blood volume.

More venous leg ulcers are healed by three-layer than by four-layer paste bandages: a randomized clinical trial

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Background: The aim of this study was to compare prospectively the number of ulcers healed, time to total healing and bandage tolerability of three- and four-layer paste bandages.
Methods: All patients with clinical evidence of venous ulceration were considered for the study. Ulcers were stratified by size into one of three groups and patients were randomized within each group to receive either three- or four-layer paste bandages. Patients with diabetes, sickle-cell disease, ankle : brachial pressure index less than 0·9, positive autoimmune serology, or ulcers smaller than 0·25 cm^2 or larger than 100 cm^2 in diameter were excluded. Complete ulcer healing was the only study endpoint. A venous aetiology was confirmed with duplex imaging, foot volumetry and venography. All patients were followed for 1 year and classified according to clinical manifestations, etiological factors, anatomic involvement and pathophysiological features (CEAP) criteria.
Results: A total of 133 patients was entered into the study; 80 per cent of patients (51 of 64) receiving three-layer bandages healed, compared with 65 per cent of those (45 of 69) having four layers ($P < 0{\cdot}05$, χ^2 test). This difference was apparent only after 16–20 weeks of treatment. The time to total healing increased with increasing ulcer size. Three-layer paste bandages were quicker to apply and better tolerated than four layers. There were more post-thrombotic legs in the four-layer group (46 *versus* 38 per cent), but half-refilling times did not differ significantly. These results were unaffected when analysis was restricted to confirmed venous ulcers.
Conclusion: Three-layer paste bandages are significantly more effective at healing venous ulcers than four-layer bandages. They are also cheaper and better tolerated. Some 20–35 per cent of venous ulcers remain unhealed at 1 year despite adequate compression.

Prognosis following venous thromboembolism in women taking combined oral contraceptives

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Background: It is widely believed that 'post-thrombotic limb' always follows deep vein thrombosis (DVT). Prognosis following both DVT and pulmonary embolism (PE) was investigated.
Methods: Some 155 women (mean age 25·5 (range 16–49) years) who developed venous thromboembolism while taking third-generation oral contraceptives were studied. The venous system was assessed by duplex imaging a mean of 4·8 years after DVT.
Results: Fourteen (15 per cent) of 96 women suffering PE died. Of the 82 surviving patients, 12 (15 per cent) had chest pain and/or dyspnoea at rest or on exertion. Of the 103 women with confirmed DVT, 59 (57 per cent) had had only calf thrombosis and 44 (43 per cent) had had iliofemoral vein thrombosis. At follow-up, 13 (22 per cent) and 21 (48 per cent) women with calf and iliofemoral thrombosis respectively had leg symptoms, including swelling, pain and lipodermatosclerosis ($P = 0{\cdot}011$). Duplex imaging was normal in 60 patients (58 per cent). There was no significant difference in leg symptoms (31 *versus* 34 per cent) or incompetence on duplex imaging (41 *versus* 42 per cent) between those who were anticoagulated for 3 months ($n = 39$) or 6 months ($n = 64$) respectively. Leg symptoms were more frequent in the 41 women with DVT discharged without elastic stockings, affecting 19 (46 per cent) compared with only 15 (24 per cent) of 62 discharged with stockings ($P = 0{\cdot}034$).
Conclusion: The majority of women regained venous patency and became asymptomatic, despite extensive DVT. Elastic stockings were often omitted despite the evidence of long-term benefit.

Improvement in walking ability, ankle pressure indices and quality of life in vascular claudication using intermittent pneumatic foot and calf compression: a randomized controlled trial

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Background: Perioperative mortality, graft failure and limitations of balloon angioplasty mitigate against active intervention for claudication. With the exception of exercise programmes, conservative treatments yield modest results. Intermittent pneumatic compression (IPC) of the foot used daily for over 3 months enhances significantly the walking ability and pressure indices of stable claudicants. This prospective randomized study evaluated the effects of IPC of the foot and calf simultaneously (IPC$_{\text{foot+calf}}$) on the walking ability, arterial haemodynamics and quality of life of patients with intermittent claudication.
Methods: Forty-one stable claudicants, meeting stringent inclusion and exclusion criteria, were randomized to receive either IPC$_{\text{foot+calf}}$ and 75 mg aspirin (group 1; $n = 21$) or 75 mg aspirin alone (group 2; $n = 20$), with stratification for diabetes and smoking. Groups matched for age, sex, initial (ICD) and absolute (ACD) claudication distance, ankle : brachial pressure index (ABPI), popliteal artery flow (Q) and quality of life (Short Form (SF) 36 questionnaire). IPC$_{\text{foot+calf}}$ (120 mmHg, three cycles per min, inflation 4 s, proximal inflate delay 1 s) was used for 2·5 h daily for 5 months consecutively. Both groups were advised to exercise unsupervised. Evaluation of patients, after randomization, included: (a) ICD and ACD on a treadmill, (b) resting and postexercise ABPIs, (c) Q using duplex imaging, and (d) quality of life. Study time-points were: baseline and 1, 2, 3, 4, 5 and 17 months. Compliance was assessed by means of a log book. Non-parametric statistical analysis was used (Wilcoxon and Mann–Whitney tests).

Results: After 5 months of $\mathrm{IPC}_{\mathrm{foot+calf}}$ median ICD, ACD, resting and postexercise ABPI in group 1 increased by 197, 212, 17 and 64 per cent (all $P < 0{\cdot}001$) respectively; changes in group 2 were all non-significant ($P > 0{\cdot}1$). On intergroup comparison at 5 months, patients in group 1 were better than those in group 2 in terms of ICD, ACD, resting and postexercise ABPI (all $P < 0{\cdot}01$). Q changes within this period were not significant in either group; neither were intergroup Q differences ($P > 0{\cdot}1$). Associated changes in the quality of life within group 1 at the end of month 5 were significant; non-significant changes were noted in group 2. At 5 months patients in group 1 enjoyed a better quality of life than those in group 2 ($P < 0{\cdot}01$). $\mathrm{IPC}_{\mathrm{foot+calf}}$ use did not result in any complications. The daily $\mathrm{IPC}_{\mathrm{foot+calf}}$ compliance (2·5 h per day) was greater than 82 per cent in the first month and greater than 85 per cent in months 2–5. One year after the end of $\mathrm{IPC}_{\mathrm{foot+calf}}$ application, patients in group 1 maintained the improved ABPI and walking benefit.

Conclusion: $\mathrm{IPC}_{\mathrm{foot+calf}}$ emerged as an effective, high-compliance, uncomplicated method for improving the walking ability and pressure indices in patients with stable claudication, with a confirmed durable outcome. These changes are associated with a significant improvement in all aspects of quality of life evaluated by the SF-36. Despite a limited benefit noted in some individuals, unsupervised exercise had a non-significant impact overall.

Randomized controlled trial of four-layer bandaging and simple venous surgery for venous ulceration

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Background: No randomized controlled trials exist to show whether simple venous surgery benefits healing or maintenance of healing of venous ulcers.

Methods: Some 121 consecutive patients with new episodes of venous ulceration were identified; 45 patients were unfit or unwilling for randomization. The remaining 76 (39 women) were assigned randomly to received a four-layer bandage ($n = 39$) or simple venous surgery ($n = 37$). All patients were followed for a minimum of 6 months. Outcome was assessed at a minimum of 6 months as healing and health-related quality of life (HRQL).

Results: The two groups had similar co-morbidity and pattern of venous incompetence. There were no major complications in either group. The healing rate was 64 per cent (25 of 39) in the conservatively treated group and 68 per cent (25 of 37) in the operated group ($P = 0{\cdot}75$, Pearson χ^2 test). There was no significant difference between time to ulcer healing in the two treatment groups (log rank statistic = 0·69, $P = 0{\cdot}41$). Patterns of venous incompetence did not affect the healing rate. There were no major differences in HRQL between the two groups.

Conclusion: This pilot study suggests that simple venous surgery gives no adjuvant benefit to four-layer bandaging in venous ulceration from the point of view of healing rate and quality of life.

Evaluation of duplex ultrasonography *versus* other investigations in the diagnosis of 'venous aetiology' in patients with leg ulcers

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Background: The aim was to compare duplex imaging, venography, foot volumetry and air plethysmography in patients with healed leg ulcers considered to be caused by venous disease to discover whether duplex scanning alone could confirm a venous aetiology. The importance of isolated reflux in a segment of the deep system below a competent valve was assessed.

Methods: A total of 125 patients with 153 healed leg ulcers was examined. An Acuson (Mountain View, California, USA) scanner was used to detect reflux lasting for more than 0·5 s in the deep, superficial and calf perforating veins; the findings were compared with those obtained with ascending venography, foot volumetry and air plethysmography.

Results:

	No. of legs with duplex reflux > 0·5 s ($n = 153$)
Isolated superficial reflux	6
Superficial reflux with incompetent perforating veins	26
Isolated incompetent perforating veins	8
Isolated deep venous reflux	11
No reflux	13

Thirteen legs showed no reflux on duplex imaging, but ten of these had abnormal foot volumetry and 12 had abnormal plethysmography. Venography showed post-thrombotic change in 26 legs, but there was evidence of deep venous scarring in only six on duplex ultrasonography. Eight of 75 legs with a normal venogram had 'complete' (thigh-to-calf) deep reflux on duplex imaging. Forty-five legs showed segmental deep reflux on duplex imaging, of which 29 had associated perforating vein incompetence. Mean half-refilling times on foot volumetry were 8·46 s for femoral and 5·84 s for popliteal reflux, compared with 3·84 s in the 33 patients who had thigh-to-calf reflux ($P < 0{\cdot}05$).

Conclusion: Absence of reflux in all venous segments on duplex imaging does not exclude a venous aetiology for ulceration. Segmental femoral and popliteal incompetence on duplex imaging is usually associated with other sites of valvular incompetence, but depresses calf function less than thigh-to-calf reflux.

Chronic venous insufficiency in the general population: clinical and duplex correlations

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Background: If operations for chronic venous insufficiency (CVI) are to be rational and cost effective, the natural history needs to be understood and patients with early disease who will progress to advanced CVI and leg ulcer need to be identified. Published data have derived largely from selected referred hospital patients. The pattern of venous disease in the general population is unknown. The aim was to determine the prevalence of CVI in the general population and to correlate clinical features with the findings on duplex ultrasonography.

Methods: A cross-section of men and women aged 18–64 years randomly selected from 12 general practices were surveyed. Subjects were screened by questionnaire, examination, photography, blood tests and continuous-wave Doppler ultrasonography. Eight segments of the deep and superficial veins were assessed for reflux by means of duplex ultrasonography.

Results: Some 1566 patients were screened (867 women of mean age 44·8 years and 699 men of mean age 45·8 years), of whom 134 were diagnosed as having CVI (Basle classification): grade 1, 95; grade 2, 19; grade 3, ten. The age-adjusted prevalence for the whole series was 3·1 per cent (2·6 per cent in men, 3·4 per cent in women). The prevalence of CVI correlated closely with age, being 15·2 per cent in men aged over 50 years and 9·0 per cent in women aged above 50 years. Heaviness, tension, swelling, aching and itching were significantly commoner in patients with CVI than in the general population. CVI was significantly associated with reflux in all deep and superficial segments. The frequency of reflux in both superficial and deep segments increased with the clinical severity of disease ($P = 0·01$). In 48·1 per cent reflux was limited to the superficial system and was thus potentially remediable.

Conclusion: CVI was common in this relatively young population. Having established the frequency of CVI and its related pattern of reflux in the general population, this cohort provides a benchmark for clinical studies and will form the basis of further longitudinal epidemiological studies.

Surgery for venous insufficiency: are venous function tests necessary?

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Background: The role of duplex imaging and measurement of ambulatory venous pressure (AVP) in the preoperative assessment of patients with venous insufficiency (VI) and primary varicose veins (VV) was investigated.

Methods: Venous incompetence was confirmed by duplex imaging in 58 legs: 38 had VI, demonstrated by eczema, oedema or pigmentation, and 20 had VV and normal skin. AVP was measured from a cannulated dorsal foot vein before and after ten tip-toe exercises. This was repeated following occlusion of the superficial veins by narrow tourniquets. Pressure relief index (PRI) was calculated as the fall in AVP in calf exercise × 90 per cent refilling time in seconds. The criterion for superficial vein surgery was doubling of PRI on superficial vein occlusion.

Results: Superficial venous incompetence (SVI) was confirmed in all legs with duplex imaging. Deep vein incompetence (DVI) was found in 17 legs (45 per cent) with VI and in two (10 per cent) of the VV legs ($P = 0·012$, χ^2 test). Venous function was normal (PRI greater than 1000) in six. Median PRI in patients with VI and VV was 177 and 289, rising to 717 and 1026 respectively after superficial vein occlusion. Initial PRI was significantly lower in patients with DVI ($P < 0·001$). PRI improved by 135 per cent in SVI and by 318 per cent in legs with DVI ($P = 0·01$). PRI did not double following superficial venous occlusion in 20 legs (35 per cent) with SVI and in three (16 per cent) with deep incompetence ($P = 0·01$).

Conclusion: Clinical examination and duplex imaging alone cannot predict who will benefit most from superficial venous surgery. AVP measurement rationalizes decision-making and may avoid unnecessary operations.

Scottish Leg Ulcer Project: a randomized trial evaluating the implementation of national guidelines

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Background: Innumerable consensus documents and guidelines have been published, but little is known about their implementation or impact. Community nurses provide more than 80 per cent of the care of patients with chronic leg ulcers. Healing rates of 50–74 per cent at 3 months have been reported in published trials. Outcomes in the community are largely unknown. National guidelines on leg ulcer care were published in 1998 by the Scottish Intercollegiate Guideline Network (SIGN), which produces evidence-based guidelines using strict criteria and methodology. The aim was to evaluate the impact of national guidelines, with or without a structured nurse training programme, on leg ulcer healing rates in the community nationwide.

Methods: Community healthcare trusts covering a population of 2·65 million were divided into 50 geographically and administratively distinct localities averaging 53 000 population, which were randomized to either SIGN guidelines (control) or guidelines plus a guideline-based nurse training programme (intervention). Data were collected from 649 caseload managers by 3-monthly censuses throughout the 2·5 years of the project. After a 6-month baseline period, guidelines were distributed and an intensive programme of training was provided throughout Scotland by a multidisciplinary team in the intervention localities for 51 link nurses, who were trained and resourced to cascade their training to approximately 1700 community nurses.

Results: Some 4413 patients with 4984 ulcerated legs were registered. The mean age of 77 years was more than a decade older than that in published trials. Multiple co-morbidities were reported. The response rate from caseload managers was 99·4 per cent, rising to 100 per cent for the rest of the study. Intercensal follow-up was complete for 98·9 per cent of patients. The baseline 3-month ulcer healing rate was 30 per cent; it remained the same throughout the subsequent 2 years, with no difference between intervention and control groups.

Conclusion: Neither national guidelines nor an intensive training programme made any impact on leg ulcer healing rates. The outcomes of leg ulcer care are poor. The delivery of care requires reorganization. The impact and implementation of consensus statements and guidelines should be evaluated.

Infrainguinal reconstruction with endoscopically harvested saphenous vein

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Background: Endoscopic saphenous vein harvesting is gaining popularity in cardiac units because of a perceived reduction in lower limb wound complications. The requirements of the cardiac surgeon for saphenous vein differ from that of the peripheral vascular surgeon in that longer individual vein grafts are required for peripheral reconstruction.

Methods: Endoscopic vein harvest has been evaluated in the reconstruction of 36 legs. Vein was harvested successfully in all cases, although major vein damage occurred in one patient. All veins were reversed and routed through a new tunnel, and used for 18 above-knee femoropopliteal bypasses, 12 below-knee femoropopliteal bypasses, four distal and two pedal grafts. Mean follow-up was 20 (range 3–36) months.

Results: There were six graft occlusions, two in the immediate postoperative period, two at 1 month and two late closures at 1 year. Three patients had wound infections, two had significant haematomas and four had problematic oedema after operation. Postoperative stay was 2–18 days, with 17 patients being discharged within 5 days and 28 within 9 days.

Conclusion: Although this technique can be used successfully for vein harvesting, the immediate impact on patient morbidity and postoperative stay is only marginal and probably does not justify the increased cost of the procedure.

Medicolegal claims for vascular problems

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Background: The continuing increase in medicolegal activity demands good risk management, and this requires knowledge of the most likely causes of litigation. This study examined 'vascular' cases notified to the Medical Defence Union (MDU) during 1990–1999, and claims initiated against the National Health Service Litigation Authority (NHSLA) since its inception in 1995.

Methods: The MDU was notified of 254 claims by 74 vascular (29 per cent) and 180 general (71 per cent) surgeons; only 35 have so far been settled. Varicose vein operations were the reason for 70 per cent of cases notified. A further 299 vascular cases were notified from primary care, of which 197 (66 per cent) involved critical limb ischaemia (80 per cent of patients had amputations and 16 per cent died), and 102 (34 per cent) involved diagnosis and treatment of aneurysms.

Results: Of 102 'vascular' claims notified to the NHSLA, 70 (69 per cent) related to arterial disease and 32 (31 per cent) to venous problems (26 varicose veins and six thromboembolism). In addition there were ten arterial and 58 varicose vein claims involving 'general' surgeons. Varicose vein claims ($n = 244$) were most often for damage to nerves ($n = 76$), incorrect or 'unsatisfactory' surgery ($n = 36$) or damage to the femoral vessels ($n = 29$). The commonest arterial claims concerned aortic surgery ($n = 45$), failure to diagnose or treat ischaemia ($n = 36$) and complications of bypass grafts ($n = 28$).

Conclusion: Varicose vein surgery is a major cause of litigation: very explicit counselling (particularly about the risk of nerve damage) and good record-keeping are required to defend these claims.

Distal anastomotic environment: the influence of intrinsic and extrinsic factors on flow structure

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Background: Improved patency of the Miller cuff may be attributable to the modification of haemodynamics at the anastomosis inhibiting the accretion of myointimal hyperplasia. The influence of the distal anastomotic environment on flow patterns may therefore have important clinical significance.

Methods: Anastomotic models of Miller cuff, end-to-side (ETS) and precuffed grafts (Distaflo™, Impra, Tempe, AZ, USA) were perfused under physiological conditions. Visualization studies and Doppler colour flow mapping (P700, Philips Medical Systems, Reigate, UK) enabled qualitative flow analysis of the influence of anastomotic geometry, configuration and outflow distribution. Intraoperative flow distribution was measured with a Doppler transit time probe. Flow within *in vivo* precuffed grafts was analysed by means of colour flow mapping and velocity profiles.

Results: ETS anastomosis demonstrated a large area of flow separation at the graft toe, except when distal outflow approached 100 per cent, when laminar flow prevailed. The Miller cuff created a cohesive vortex within the proximal anastomosis, with reduced areas of flow separation. Outflow distribution had little effect upon the integrity of this vortex, although helical flow occurred in the distal vessel when proximal run-off was occluded. Cuff geometry, expressed as aspect ratio (cuff length : height) was important, with long and low cuffs demonstrating detrimental flow structures, including complex short-lived vortices and large areas of separation. The precuffed model produced a robust vortex, resistant to flow distribution. *In vitro* Doppler images of the vortex were reproduced accurately in 77 per cent of patients with precuffed grafts *in situ* ($n = 32$). Mean intraoperative flow distributions of

76 per cent distal : 24 per cent proximal in infragenicular grafts were significantly different from anticipated ratios of 50 : 50 and 100 : 0 ($P < 0.001$, single-sample t test). In above-knee grafts, however, distribution approached purely distal flow (mean 85 : 15 *versus* 100 : 0; $P = 0.046$).

Conclusion: Anastomotic flow structures are determined by the geometry of the anastomosis and the relative flow distribution proximally and distally in the recipient artery. A cuffed configuration of anastomosis is likely to be of most benefit when there is substantial flow proximally as well as distally in the run-off vessel, a situation that applies most often in infragenicular reconstruction. In addition, variable cuff geometry may detract from the full potential of the Miller cuff. A precuffed graft of optimum geometry may negate this concern, with the majority of patients demonstrating accurate replication of potentially beneficial flow patterns.

Association between hyperhomocysteinaemia and abdominal aortic aneurysm

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Background: Hyperhomocysteinaemia is associated with occlusive vascular disease. *In vitro* evidence has demonstrated the induction of a serine elastase by homocysteine in vascular smooth muscle. Anecdotal evidence from case reports and post-mortem studies has suggested an association with abdominal aortic aneurysm (AAA). The aim was to determine the prevalence of hyperhomocysteinaemia in patients with AAA.

Methods: Some 120 subjects (60 controls and 60 patients with AAA) were studied prospectively. Epidemiological, clinical and haematological data were collected. Patients were defined as having AAA if ultrasonographic measurement of the aorta was greater than 4·5 cm. Those with evidence of occlusive peripheral vascular disease or an ankle : brachial pressure index lower than 0·8 were excluded. Homocysteine was measured with a commercial high-pressure liquid chromatography analyser. The reference range from age-matched controls was 8·9–14·3 μmol l^{-1}.

Results: The median(s.d.) value of homocysteine for patients was significantly higher than that for the control group: 13·1(7·88) *versus* 10·9(5·07) μmol l^{-1} ($P = 0.03$, Mann–Whitney U test). Hyperhomocysteinaemia (homocysteine concentration greater than 14·3 μmol l^{-1}) was present in 48 per cent of patients with AAA, compared with 24 per cent of the control population ($P < 0.01$, χ^2 test). There were no significant differences between groups with regard to age, folate levels, vitamin B_{12} concentration or renal function.

Conclusion: These results strongly suggest an association between hyperhomocysteinaemia and AAA. If studies currently ongoing demonstrate a causal relationship between hyperhomocysteinaemia and vascular disease progression, it raises the possibility of treating small aneurysms with vitamin supplementation to slow their growth.

A single ultrasonographic scan at age 65 years excludes 95 per cent of men from future aneurysm risk

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Background: In 1988, 236 men, then aged 65 or 66 years, underwent an abdominal ultrasonographic scan as part of a pilot study for an aneurysm screening programme; 223 (95 per cent) had an aortic diameter of 25 mm or less, and form the main study group.

Methods: This group was followed with repeat ultrasonography in 1993 and 2000. Eight men (4 per cent) were lost to follow-up or refused further scanning, but all are known to be still alive. Eighty-six men (39 per cent) died during the 12-year follow-up. Causes of death were investigated. None was related to abdominal aortic aneurysm (AAA). Some 129 men (58 per cent) had all three ultrasonographic scans, including some arranged in other hospitals or performed with a portable scanner at a home visit. Mean(s.e.m.) aortic diameter for this group was 18·9(2·3) mm in 1988, 19·0(2·6) mm in 1993 and 20·2(3·8) mm in 2000.

Results: At the scan in 2000, four men had an aortic diameter greater than 30 mm (32, 34, 34 and 36 mm respectively). In contrast, of the 13 men with an aortic diameter greater than 25 mm in 1988, three have undergone elective aneurysm repair, eight have died from causes unrelated to AAA and two remain under ultrasonographic surveillance.

Conclusion: Using an aortic diameter threshold of 25 mm, a single ultrasonographic scan at the age of 65 years is able to exclude 95 per cent of men who appear extremely unlikely ever to develop a clinically significant aortic aneurysm and to identify the 5 per cent who require further follow-up.

Myocardial infarction following aortic surgery: a comparison of cardiac troponin I and creatine kinase ratio

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Background: Perioperative myocardial infarction may be underdiagnosed and/or misdiagnosed because World Health Organization criteria are often not met and creatinine kinase/creatinine kinase-muscle band (CK/CK-MB) ratios can be difficult to interpret. Cardiac troponin (cTn) I is the most sensitive and specific marker of myocardial cell necrosis but is not yet widely available. The aim was to compare cTnI and CK/CK-MB ratios in the diagnosis of myocardial infarction following aortic surgery.

Methods: This prospective study included 58 patients undergoing elective (27 aneurysm, seven occlusive) or emergency (24 ruptured aneurysms) aortic surgery. cTnI concentration was measured before operation and 6, 24, 48, 72 and 96 h after surgery. CK and CK-MB levels were measured where cTnI was detectable. Clinical and electrocardiographically detected cardiac events were documented prospectively.

Results:

	Emergency ($n = 24$)	Elective ($n = 34$)
cTnI rise > 0·5 ng ml^{-1}	13	9
CK/CK-MB rise (ratio > 5%) where cTnI detected	4	0
cTnI rise and cardiac event	8	4
cTnI rise with no cardiac event	5	5

Conclusion: More than half of patients undergoing emergency, and more than a quarter of those undergoing elective, aortic surgery suffer myocardial necrosis as determined by cTnI concentration. This is accompanied by an increased CK/CK-MB ratio in less than one-fifth of cases.

Mortality rates from ruptured abdominal aortic aneurysms in England

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Background: Over the past 10 years significant advances have been made in understanding the natural history and pathophysiology of aortic aneurysm disease. Despite a rapid improvement in alternative repair techniques, surgery for abdominal aortic aneurysm (AAA) remains the standard method of treatment. The aim of this study was to evaluate the efficacy of this treatment at a national level.

Methods: Data for elective and emergency AAA procedures performed in England between 1989 and 1998 were obtained from the Department of Health Hospital Episode Statistics. Data for deaths secondary to ruptured and non-ruptured AAA in England for the same period were obtained from the Office of National Statistics. All figures represent age-adjusted incidence per 100 000 population.

Results:

	Age-adjusted incidence per 100 000 population	
	1989	1998
Elective AAA performed	5·6	9·6
Emergency AAA performed	3·6	4·7
Death		
Non-ruptured AAA	2·1	2·4
Ruptured AAA	13·0	14·5

The rise in elective and emergency AAA repair rates affected mainly men rather than women. The rise in death rates from ruptured AAA was 30·3 per cent in women and 2·0 per cent in men.

Conclusion: Despite a considerable increase in elective AAA repair procedures in England, deaths from ruptured AAA continue to rise. These findings highlight the need for an efficient national strategy for improving the outcome of patients with AAA.

P-selectin deficiency is protective against remote organ injury in a model of ruptured abdominal aortic aneurysm

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Background: Multisystem organ failure (MSOF) accounts for 50–60 per cent of postoperative deaths following repair of ruptured abdominal aortic aneurysm (AAA). A murine model is described in which the combined insults of hypotension and aortic clamping reproduce the physiological changes during repair of ruptured AAA. The resulting remote organ injury (the hallmark of MSOF) is prevented in the absence of the adhesion molecule P-selectin, which mediates neutrophil–endothelial interaction.

Methods: C57BL6 wild-type mice ($n = 4$) and mice constitutively unable to express P-selectin ($P^{-/-}$) ($n = 4$) were subjected to 60 min of controlled hypotension followed by cross-clamping of the infrarenal aorta for 60 min, reinfusion of shed blood and then 60 min of reperfusion. Controls ($n = 16$) were sham-operated, had hypotension only or clamp/reperfusion only. Lungs and kidneys were harvested and assayed for the neutrophil-specific marker myeloperoxidase (MPO), which indicates inflammatory infiltrate in the tissue.

Results: MPO levels in the organs of C57BL6 mice subjected to hypotension and aortic clamping were 50 times greater than those in sham-operated mice. MPO levels in sham-operated $P^{-/-}$ animals were similar to those in sham-operated C57BL6 mice. MPO levels in the lungs and kidneys of $P^{-/-}$ mice subjected to hypotension and aortic clamping were unchanged from those in sham-operated $P^{-/-}$ mice.

Conclusion: The combined effects of hypotension and infrarenal aortic clamping, followed by reperfusion, are synergistic. This gives rise to a profound early inflammatory reaction in tissues remote from the site of ischaemia–reperfusion, which is likely to contribute towards clinical MSOF after ruptured AAA repair. Absence of the adhesion molecule P-selectin protects against this remote organ injury.

Mortality following aortic surgery as a possible indicator of clinical performance

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Background: The mortality rate following aortic surgery has been suggested as a possible indicator of clinical performance.

Methods: Routine hospital data on mortality following aortic surgery were collected for a 2-year interval in the Trent region. Procedural and diagnostic codes, mode of admission, district of residence, treatment and specialty data were analysed and compared with audit data and the Operating Theatre Information System.

Results: Inaccuracies in coding using the HRG (Health Resource Group) codes meant that 21·4 per cent of elective aortic cases (HRG Q01) were probably emergencies and 26 per cent of probable emergency ruptures were not coded as vascular emergencies. The HRG system does not identify complex procedures carried out in specialist centres, thereby distorting the overall mortality figures. Case mix and patient selection introduced a bias, apparent between tertiary and district general hospitals, with higher-risk elective and lower-risk emergency cases at tertiary referral centres. For patients aged over 80 years, two districts undertook no elective aortic surgery, and the rates for emergency surgery varied between 16 and 25 per cent in the districts and 77 per cent in the tertiary centre. After correction for these factors, there remains significant variation in mortality rates between tertiary referral centres and the district hospitals (*Table*).

	Mortality rate (%)	
	Elective	Emergency
Tertiary centre	4·2 (0·9–7·4)	30·4 (22·3–38·5)
District general	10·5 (5·5–15·5)	59·4 (49·8–69·0)

Conclusion: Some of the difficulties in using crude mortality rates as an indicator of performance have been highlighted. They are subject to bias and distortions owing to the collection of incorrect information, patient selection differences between hospitals, case-mix differences and tertiary transfer of complicated cases. Other case-mix factors can be accounted for only with more detailed collection of clinical data such as POSSUM (Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity) scores. However, there remains considerable and worrying variation in selection and outcomes of patients undergoing aortic surgery.

Renal disease, age and outcome after aortic aneursym repair

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Background: The safety of conventional aneurysm repair is undergoing increased scrutiny as less invasive methods are developed, certain high-risk groups identified and the evidence for the risk of rupture is refined. An understanding of the relationship between preoperative risk factors and outcome is particularly important in elderly patients requiring a prophylactic operation.

Methods: Risk factors (extent of aneurysm, ischaemic heart disease, renal function, hypertension, diabetes, serum cholesterol concentration, age and sex) were studied in 393 consecutive patients undergoing elective juxtarenal and infrarenal aneurysm repair between 1993 and 1999 (inclusive), and were related to hospital mortality.

Results: The overall mortality rate was 5·1 per cent (20 of 393). Multivariate logistic regression analysis revealed that age and creatinine concentration were independent risk factors for in-hospital mortality. Extent of aneurysm was not an independent risk factor, nor was a history of myocardial ischaemia, sex, hypertension, diabetes or serum cholesterol level. The comparative risk related to age and serum creatinine concentration is shown in the *Table*.

Age (years)	Creatinine (μmol l^{-1})	Mortality rate (%)
<70	>60	0·5 (0·0–1·1)
>70	<120	4·7 (2·5–6·9)
>70	121–180	14·1 (4·5–23·7)
>70	>180	16·7 (0·0–34·7)

Values in parentheses are 95 per cent confidence intervals (c.i.)

Creatinine level had no influence on outcome in patients aged under 70 years. However, in those over 70 years of age, an increase in creatinine concentration of 10 μmol l^{-1} increased the relative risk by 0·1 (95 per cent c.i. 0·01–0·18). Increasing age by 10 years increased the relative risk by 1·5 (95 per cent c.i. 0·6–2·4).

Conclusion: Advances in preoperative and perioperative care appear to have reduced the significance of ischaemic heart disease and juxtarenal repair so that age and renal disease are currently major determinants of survival. In aneurysms of less than 7 cm in diameter, where the risk of rupture is less than 10 per cent per year, the natural history of the disease in elderly patients with renal failure appears to be more benign than the treatment.

Randomized prospective comparison of postoperative pain control and respiratory complications following midline or transverse laparotomy for aortic surgery

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Background: Transverse abdominal incisions are thought to be less painful and followed by fewer pulmonary complications than midline incisions, but reports remain controversial. This study compared midline and transverse incisions for elective transabdominal aortic aneurysm repair with respect to postoperative pain, respiratory function and pulmonary complications.

Methods: Sixty patients were randomized to midline laparotomy and transverse incisions, and evaluated before and after operation for 7 days at regular intervals. Analgesia was provided via a thoracic epidural and pain scores were recorded by means of a visual analogue scale. Respiratory function (peak expiratory flow rate, forced expiratory volume in 1 s and forced vital capacity) and pulmonary complications were monitored as well as patient characteristics, operating time, blood loss, operative exposure, and length of stay on the intensive care unit (ITU) and in hospital.

Results: The two groups included a similar number of patients ($n = 30$ per group) and basic characteristics such as age and preoperative risk factors. Linear analogue pain scores were significantly lower in the transverse group of patients ($P < 0{\cdot}001$). There was no significant difference between the two groups with regard to postoperative ventilatory function and respiratory complications as well as analgesic requirements, operating time, blood loss, and length of ITU and hospital stay.

Conclusion: The direction of incision does not seem to influence the incidence of respiratory complications. However, a transverse incision in combination with a high epidural analgesia seems to offer better postoperative pain control.

Risk assessment and outcome in endoluminal aortic aneursym repair: effect of the learning curve

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Background: The aim was to investigate the effect of risk categorization on outcome from endoluminal aneurysm repair (ER) and to note changes in outcome with increasing experience.

Methods: Clinical and operative details of the first 70 patients undergoing ER (1995–1999) were analysed. American Society of Anesthesiologists (ASA) grade and POSSUM (Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity) score were determined. The cohort was divided arbitrarily into two groups: group 1 included the first 35 patients, and group 2 the second 35.

Results: Median age was 73 (55–93) years; 65 of the patients were men. The overall 30-day mortality rate was seven of 70 (10 per cent). No deaths were directly attributable to the anaesthesia; four deaths were due to myocardial infarction. There was no difference in ASA grade or POSSUM score between the groups. Fourteen patients (20 per cent) were converted to open surgery, nine during the same period of anaesthesia as the ER.

	Group 1 ($n = 35$)	Group 2 ($n = 35$)
ASA III–IV	28	29
Converted	13	1
Conversion mortality	3	1
Successful ER	22	34
ER mortality	1	2
Overall mortality	4	3

The odds ratio (OR) for conversion comparing groups 1 and 2 was significant, but the OR for total mortality and for mortality in those who had successful ER was not significant.

Conclusion: ASA grading and POSSUM scoring has not changed with time. There was a learning curve, due largely to improvement in surgical technique. Four of the 14 patients undergoing conversion died; only one conversion occurred in the later experience. However, there was no statistically significant difference in total or ER mortality.

Registry of Endovascular Treatment of Abdominal Aortic Aneurysms (RETA): the fate of patients with primary endoleaks

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Background: The aim was to present the follow-up data of patients with a primary endoleak identified in the periprocedural period to establish the consequences of these endoleaks.

Methods: There were 123 primary endoleaks in the 1000 operations logged in the Registry of Endovascular Treatment of Abdominal Aortic Aneurysms (RETA) database, visualized either immediately after the procedure or at 30-day computed tomography. The sites of these were: collateral, 42 (34 per cent); proximal anastomotic (PA), 41 (33 per cent); distal anastomotic (DA), 19 (15 per cent); midgraft, 12 (10 per cent); occluder, three (2 per cent); and site not stated in six (5 per cent). The fate of these endoleaks was examined from available follow-up data.

Results: Nine patients (22 per cent) with PA endoleaks died from rupture ($n = 3$) or following surgery for the endoleak ($n = 6$). Eleven patients had persistent primary PA endoleak with or without treatment; three of these patients had rupture. Others were treated successfully with surgery, proximal cuffs or angioplasty of the proximal anastomosis. Twenty-two collateral endoleaks (52 per cent) resolved spontaneously at 30 days. There were no ruptures at follow-up. Seven of the 19 DA endoleaks resolved spontaneously by 30 days and four had further endovascular treatment before discharge. Of the eight persistent endoleaks, three resolved spontaneously and three had endovascular treatment. There were no ruptures at follow-up. Two of the three occluder endoleaks resolved spontaneously; the other patient died suddenly from an unknown cause. Nine of the 12 midgraft endoleaks resolved by 30 days, and one had resolved spontaneously at 1 year; again there were no ruptures in this group.

Conclusion: The presence of a PA endoleak justifies an aggressive approach to treatment because of their association with aneurysm rupture. However, open surgical treatments carry a significant mortality rate. Other endoleaks follow a more benign course, and many will resolve spontaneously.

Midterm follow-up of 1000 patients in the Registry of Endovascular Treatment of Abdominal Aortic Aneurysms (RETA)

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Background: The aim was to present the midterm follow-up data of patients in the Registry of Endovascular Treatment of Abdominal Aortic Aneurysms (RETA).

Methods: RETA now has a cohort of 1000 registered patients. Follow-up data are available for 483 patients at 1 year (80·8 per cent follow-up rate), 191 at 2 years (78·0 per cent follow-up rate) and 64 at 3 years (64·0 per cent follow-up rate).

Results: The mortality rates were 10·8, 12·6 and 6·3 per cent at 1, 2 and 3 years' follow-up respectively. The majority of deaths at follow-up were unrelated to the endovascular aneurysm repair. However, ruptures have occurred, with five (1·0 per cent) occurring in the first year of follow-up and three (1·6 per cent) reported in the second year of follow-up. This gives a cumulative risk of rupture of 1·0 per cent at 1 year and 2·6 per cent at 2 and 3 years. Three of the ruptures had persisting primary proximal endoleaks and two had documented secondary endoleaks. Complications related to the aneurysm or device occurred in 11·1, 14·8 and 12·8 per cent of cases at 1, 2 and 3 years' follow-up. The commonest problems were secondary endoleaks, although most of these had successful endovascular treatment. Graft or limb occlusions were the next most common problems. Follow-up of patients having secondary procedures with endovascular treatment suggests these treatments are durable, although the numbers at present are small. The cumulative endoleak-free survival rate was 73·4, 57·9 and 49·9 per cent, and the cumulative freedom from endoleak rate was 88·3, 81·2 and 75·6 per cent at 1, 2 and 3 years' follow-up respectively.

Conclusion: Most deaths occurring at follow-up are not related to the aortic aneursyms. Ruptures have occurred, some related to primary proximal type I endoleaks. Others may be related to secondary endoleaks that have not been detected. Late complications related to the device or aneurysm occur at a rate of about 10 per cent per year. Most frequently these are new endoleaks and are amenable to endovascular treatment, but recurrence may occur, so continued surveillance is necessary.

Endothelial integrity and nitric oxide synthase sources are better maintained in saphenous vein harvested by a 'no-touch' technique

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Background: The saphenous vein (SV) is a commonly used conduit in bypass procedures. Early graft occlusion rates are greater than 20 per cent in both infrainguinal vein grafts and coronary artery bypass grafts (CABGs). Contributing factors include adventitial and endothelial damage, which may reduce nitric oxide availability in grafts. Nitric oxide has important vasorelaxant and thromboresistant properties beneficial to graft patency. Conventionally, during SV harvest, the perivascular tissue is stripped and the graft distended. A 'no-touch' technique has been described in which the SV is harvested together with a cushion of surrounding tissue without vein distension. This study compared endothelial integrity and the potential role of nitric oxide synthase (NOS) in segments of SV harvested by the two techniques.

Methods: SV was harvested from ten patients undergoing CABG. Distal and proximal ends of the SV were harvested using the no-touch technique, while the middle portion was stripped of the adventitia and distended. Sections of SV were cut and endothelial integrity was assessed with CD31 immunohistochemistry and quantified by morphometric analysis. Putative NOS was identified by reduced nicotinamide adenine dinucleotide phosphate (NADPH)–diaphorase histochemistry and autoradiographic localization of [^{3}H]L-N^G-nitroarginine binding.

Results: More dense CD31 staining was seen on the luminal aspect and vasa vasorum of vessels harvested by the no-touch technique. Morphometric analysis revealed a significant reduction in luminal CD31 staining in conventional compared with no-touch grafts ($P < 0{\cdot}05$, Student's t test). NADPH staining was almost continuous on the luminal aspect, and was also present in the adventitia of no-touch vessels, compared with poor staining of conventionally harvested vessels. The pattern of NADPH staining corresponded to endothelial cells lining the vessel lumen as well as vasa vasorum and paravascular nerves in the adventitia. Autoradiographic analysis of specific [^{3}H]nitroarginine binding also showed greater binding in the no-touch vessels.

Conclusion: Endothelial integrity is better maintained by the no-touch technique. NOS sources on the endothelium and adventitia are preserved, suggesting that nitric oxide availability is retained by these grafts. This technique may therefore lead to improved early patency rates of SV grafts in bypass surgery.

Combined effects of aspirin and the novel antiplatelet agent clopidogrel on platelet function *in vivo* and *in vitro*

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Background: The platelet adenosine 5′-diphosphate (ADP) receptor antagonist clopidogrel has proved an effective antiplatelet agent in the prevention of arterial thrombosis. In the vast majority of studies clopidogrel has been used as an alternative to aspirin, but the widespread use of aspirin, and the different modes of actions of the two drugs, makes it important to determine the safety and efficacy of using both drugs in combination. This study reports the effect of this drug combination on bleeding times and platelet function in humans.

Methods: The study was conducted in normal, healthy subjects to evaluate the effects of different doses of clopidogrel on bleeding time, platelet aggregation and activation, above a baseline of standard aspirin therapy. Seven normal men (mean age 30 years) were given aspirin (150 mg) for 3 days. Subjects received clopidogrel (75 mg) at 24 and 48 h, followed by a third dose of clopidogrel (300 mg) on day 3.

Results:

	Baseline	Aspirin alone	Aspirin + low-dose clopidogrel	Aspirin + high-dose clopidogrel
Bleeding time (min)	5·1	7·5	17·5	24·9
Aggregation in response to ADP (%)	72	48	35	25
Fibrinogen binding in response to ADP (%)	64	50	40	24

The combination of aspirin plus clopidogrel leads to a significant reduction in platelet function relative to aspirin alone ($P < 0{\cdot}05$), and is associated with a significant increase in the bleeding time ($P < 0{\cdot}05$). The response to collagen was similarly affected. Platelet fibrinogen binding in response to both ADP and thrombospondin-related adhesive protein was reduced only partially by aspirin, but significantly reduced by both doses of clopidogrel ($P < 0{\cdot}05$ for all). P-selectin expression in response to both agonists was also reduced, but not significantly. Basal levels of fibrinogen binding, P-selectin, glycoprotein (GP) IIb–IIIa and GPIb expression were not affected by treatment.

Conclusion: Blocking both the cyclo-oxygenase and ADP pathways of platelet activation has a profound effect on platelet response to agonists, which may offer significant potential benefit in preventing thrombotic events relative to aspirin alone. Achieving the correct balance between haemostasis and thrombosis with these useful agents will require further study.

Reduction of vascular smooth muscle cell proliferation by immunomodulation

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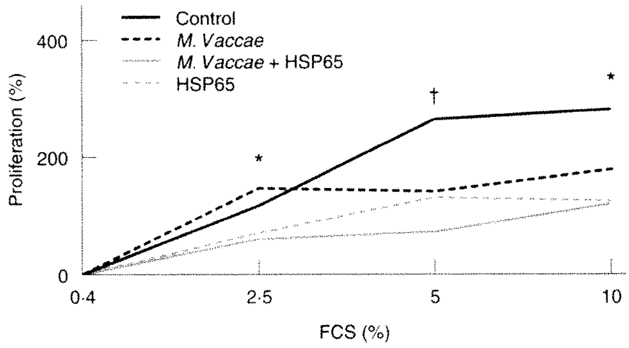
Background: Immunological factors may play an important role in mediating the progression of atherosclerosis and myointimal hyperplasia, with heat shock proteins being implicated as possible autoantigens. The authors have shown previously that immunomodulation can reduce vascular smooth muscle cell (vSMC) proliferation following balloon injury to rat carotid arteries. The aim of the present study was to examine the effects of immunomodulatory agents on the proliferation of rat aortic vSMCs remote from the area of balloon injury. The agents used were SRL172 (heat-killed *Mycobacterium vaccae*) and heat shock protein 65 kDa (HSP65) in Freund's incomplete adjuvant. Both these agents are known to influence T-cell responses.

Methods: Male Sprague–Dawley rats were used. All immunizations were given subcutaneously. Four groups were studied (ten animals in each group): group 1 animals were immunized with normal saline, group 2 received SRL172, group 3 SRL172 and HSP65–Freund's, and group 4 HSP65–Freund's. Three immunizations were performed as well as carotid balloon injury. Three animals died, leaving 37 for analysis. Some 5 weeks later the animals were killed and the aorta was harvested. Standard explant techniques were applied to grow aortic vSMCs until confluency, passaged three times, quiesced, and fetal calf serum (FCS) of varying concentrations (0·4–10 per cent) was then added, incubated for another 48 h and cell counts carried out.

Results: The proliferation rate of aortic vSMCs in the control group was significantly greater than that in the other study groups (*Fig.*). While all the treatment groups had significantly less proliferation compared with the control group ($^{*}P < 0{\cdot}05$, $^{\dagger}P < 0{\cdot}01$, Mann–Whitney U test), no statistically significant differences existed between any of the study groups.



Conclusion: Immunomodulation may result in a reduction of vSMC proliferation. Although the precise mechanisms involved are unclear, these results are in concordance with previous findings that T-cell immunomodulation decreases the development of myointimal hyperplasia after injury, and suggest that a fundamental phenotypic shift has been produced by these immunizations.

Systemic levels of plasmin–antiplasmin complexes are correlated with the expansion rate of small abdominal aortic aneurysms

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Background: The cystatine proteolytic system, the serine proteolytic system and the metallodependent proteolytic system have all been reported to be involved in the matrix degradation of the aortic wall, causing abdominal aortic aneurysm (AAA). Plasmin is a common activator of all three systems and could theoretically be involved in the pathogenesis of AAA by activating all three systems. However, plasmin is immediately inactivated by antiplasmin, forming plasmin–antiplasmin (PAP) complexes when it reaches the circulation. This study was designed to assess whether the systemic levels of PAP complex in conservatively treated patients with AAA could be related to the natural history of AAA.

Methods: In 1994, 112 of 141 men with AAA (greater than 3 cm) diagnosed by population screening were interviewed, examined, and had blood samples taken and prepared for serum and ethylenediamine tetra-acetic acid plasma by a standard method. The serum and plasma were frozen at −21°C until analysis. Of the 112 patients, 99 were followed with annual control scans and blood pressure measurements for 1–5 (mean 2·5) years, and were referred for operation if the AAA exceeded 5 cm in diameter. Of the 99 patients, a random sample of 70 had their level of PAP complexes determined (Dade Behring, Rødovre, Denmark). Furthermore, the level of serum elastin peptides (SEPs) was determined by enzyme-linked immunosorbent assay. Spearman's rank sum correlation test, multivariate linear regression analysis and receiver–operator characteristic (ROC) curve analysis were used for statistical analysis (SPSS 10.0; SPSS, Chicago, Illinois, USA).

Results: The level of PAP complex was positively correlated with annual expansion rate ($r = 0{\cdot}29$, $P = 0{\cdot}01$), but not with the initial AAA size ($r = 0{\cdot}17$, $P = 0{\cdot}16$) or SEP ($r = 0{\cdot}04$, $P = 0{\cdot}77$). The significant association to expansion persisted after adjustment for initial AAA size, SEP and smoking. Furthermore, the level of PAP complex was significantly predictive for AAAs expanding to operation recommendable size (area under ROC curve 65 per cent), with an optimal sensitivity and specificity of 65 and 67 per cent respectively. SEP level was also significantly predictive for AAAs expanding to operation recommendable size (area under ROC curve 56 per cent), with an optimal sensitivity and specificity of 56 and 57 per cent.

Conclusion: The progression of AAA seems to be caused by a general activation of the proteolytic systems involving plasmin and not by genetic or environmental factors causing increased activation of specific proteases or decreased activity of their specific inhibitors. Furthermore, the level of PAP complex in patients with an aneurysm seems to have a better and independently predictive value of the natural history of AAA, compared with the best serological predictor known to date, the serum level of elastin peptides.

Role of *Chlamydia pneumoniae* in an experimental animal model of aneurysm formation

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Background: *Chlamydia pneumoniae* has been implicated in the pathogenesis of vascular disease. *C. pneumoniae* DNA is present in 40–50 per cent of abdominal aortic aneurysm biopsies. This study investigated whether *C. pneumoniae* has a causal role in experimental aortic dilatation.

Methods: Experimental aneurysms were established in cholesterol-fed rabbits by periaortic application of calcium chloride solution and a combination of thioglycollate (a non-specific macrophage activator) or *C. pneumoniae* (live, formalin fixed or heat inactivated at 10^8 organisms per ml). After 3 weeks, aortic diameter was measured and aortas were harvested for analysis of macrophage counts. *C. pneumoniae* DNA was measured by polymerase chain reaction and *C. pneumoniae* antigens (both membrane and heat shock protein 60) were determined by immunostaining.

Results: Live or formalin-fixed *C. pneumoniae* at concentrations of 10^8 organisms per ml mimicked the effects of thioglycollate to produce aortic dilatation associated with macrophage influx. Lower concentrations of *C. pneumoniae* had a minimal effect.

Substance applied to aorta	Increase in aortic diameter (%)	*C. pneumoniae* DNA positive	*C. pneumoniae* antigen positive	Macrophage count per unit area
Calcium chloride only (control)	19(7)	0 of 6	—	5·61(6·4)
Thioglycollate	112(19)*	0 of 8	—	29·6(45)*
C. pneumoniae				
Live	125(25)*	2 of 4	Yes	342(144)*
Formalin fixed	98(198)*	2 of 5	Yes	143(69)*
Heat inactivated	54(16)*	0 of 4	No	26·6(15)*

*$P < 0{\cdot}05$ *versus* control (analysis of variance)

Conclusion: In this experimental study, high doses of *C. pneumoniae* membrane antigens stimulated macrophage influx and aortic dilatation. Lipopolysaccharide had a lesser effect. *C. pneumoniae* antigens could contribute to an *in vivo* aggregate pathogen burden by provoking an inflammatory response.

Enhanced critical care improves the mortality rate following elective aneurysm repair

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Background: In a previous study performed at this centre (1994–1997) to document the impact of instituting an endovascular programme, the mortality rate for elective infrarenal aneurysm repair was unacceptable (16 per cent). In an attempt to reduce this complication rate, two fundamental changes in practice were instituted. First, patients were selected and counselled for operation on the basis of a physiological scoring system, POSSUM (Physiological and Operative Surgical Score for the enUmeration of Mortality and morbidity). Second, patients were admitted to the critical care unit for at least 3 days after operation, before discharge to the ward. The aim of the study was to audit the result of these changes.

Methods: Data were collected prospectively for all patients admitted for elective aneurysm repair between November 1998 and January 2000. POSSUM score, postoperative mortality and morbidity, and intensive care unit (ITU) or high dependency unit stay were compared between historical controls (1994–1997) and operations performed after the change in practice.

Results: The results are tabulated below as median values.

	Historical study ($n = 104$)	Present study ($n = 47$)	P*
POSSUM	19	18	0·268
ITU stay (days)	1·0	3·0	< 0·001
Mortality rate (%)	16	4	< 0·001
Morbidity rate (%)	28	17	< 0·001
Unplanned ITU return	8	11	< 0·001

*χ^2 and Mann–Whitney *U* tests

Comparison between the two groups demonstrated that after changes in referral practice, the perioperative mortality rate improved significantly from 16 to 4 per cent. Comparison of the patient cohorts demonstrated no significant differences in preoperative physiological status.

Conclusion: These data demonstrate that defined changes in the perioperative management of patients undergoing elective aneurysm surgery may favourably affect mortality. As there was no difference in POSSUM scores between the two groups, it is likely that the improved outcome reflects more intensive postoperative care.

Autologous thrombin-induced thrombosis of pseudoaneurysms

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Background: This study was designed to evaluate the use of autologous thrombin (as opposed to commercial bovine thrombin) in the percutaneous obliteration of postcatheterization femoral pseudoaneurysms.

Methods: Ten consecutive patients with a symptomatic femoral pseudoaneurysm following cardiac catheterization underwent duplex assessment. All ten pseudoaneurysms were at least 2 cm in the longest axis. Autologous thrombin was isolated from 60 ml blood, under sterile conditions. The autologous thrombin was injected into the cavity of the pseudoaneurysm under ultrasonographic guidance. The progression of thrombosis was monitored throughout with ultrasonography. After the procedure, the femoral arteries were examined for thrombosis propagation or embolization. The foot pulses and ankle pressures were checked. Samples of the thrombin isolates were analysed to quantify thrombin activity. Duplex assessment was repeated at 6 weeks.

Results: All ten patients had successful thrombosis of the pseudoaneurysm, although three required repeat thrombin injections within 24 h. No long-term symptoms were identified relating to the thrombosis and no patient required surgery. There was no evidence of recanalization at 6 weeks on duplex imaging, and no signs of infection.

Conclusion: Autologous thrombin-induced thrombosis of pseudoaneurysms is a simple, safe, painless and inexpensive procedure. This novel approach, which uses the patient's own thrombin, is cheaper than bovine thrombin; it also avoids the risk of viral contamination or anaphylaxis from commercial thrombin.

Successful subintimal angioplasty for leg ischaemia is dependent on length of occlusion, not site of lesion

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Background: The development of subintimal angioplasty offers an endovascular approach to the treatment of long occlusions not suitable for conventional transluminal angioplasty; it remains, however, the remit of relatively few radiologists in specialist centres. The authors have adopted the technique in view of promising published results.

Methods: Between May 1997 and July 2000, 50 patients had attempted subintimal angioplasty (median age 71 (interquartile range (i.q.r.) 61–80) years). Patients were divided into two groups by length of occlusion; 26 patients (group 1) had occlusions greater than 10 cm in length (iliac, one; superficial femory artery (SFA), 24; crural, one) and 24 patients (group 2) had occlusions of less than 10 cm (iliac, five; SFA, five; popliteal, nine; crural, five). The primary technical success rate, ankle : brachial pressure index (ABPI) before and after the procedure, complication rate and symptomatic improvement were recorded for both groups.

Results: The groups were well matched for age and indication for intervention. Primary technical success was significantly better for occlusions of less than 10 cm than for the longer lesions (83 *versus* 50 per cent; $P < 0.01$) with corresponding significantly greater rises in ABPI ($P < 0.05$). Complications included one death in each group, one amputation in group 2 and six in group 1, all after failed salvage grafts.

	Group 1 (> 10 cm)	Group 2 (< 10 cm)	P
Technical success	13 of 26	20 of 24	< 0·01*
Median (i.q.r.) ABPI change	0·135 (– 0·07 to 0·23)	0·24 (0·145–0·355)	0·046†

*c^2 test; †Mann–Whitney *U* test

Conclusion: Subintimal angioplasty gives excellent results for occlusions of less than 10 cm in length irrespective of arterial site. Results for longer lesions are poor, with failed subintimal angioplasty often precipitating urgent distal vascular reconstruction and associated high risk of major amputation.

Impact of subintimal angioplasty on treatment of critical leg ischaemia

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Background: Distal bypass for critical leg ischaemia (CLI) is technically demanding and a physiological challenge to the patient. Angioplasty offers an attractive alternative, the application of which may be extended by subintimal techniques. This study reports on the immediate success of subintimal angioplasty and its impact on workload in this unit since the introduction of the technique in 1997.

Methods: This was a retrospective review of a consecutive series of 166 legs (156 patients) with CLI treated by subintimal angioplasty from 1997 to 1999. Society for Vascular Surgery and International Society for Cardiovascular Surgery criteria were used to determine clinical status and patency.

Results: From 1997 to 1998 the rate of subintimal angioplasty increased, with a corresponding reduction in major amputation and surgery rates ($P < 0\cdot001$, χ^2 test). The increase in surgical reconstruction in 1999 could reflect delayed treatment of patients with late occlusion of a previously dilated segment.

	1996	1997	1998	1999
Surgical reconstruction for CLI	104 (71·2)	104 (59·8)	70 (36·5)	114 (50·4)
Primary amputation	42 (28·8)	60 (34·5)	41 (21·4)	37 (16·4)
Subintimal angioplasty	0 (0)	10 (5·7)	81 (42·2)	75 (33·2)
Total	146	174	192	226

Values in parentheses are percentages

The technical success rate of subintimal angioplasty was 84·9 per cent (25 primary failures). Twelve proceeded to bypass surgery, with one occluded graft subsequently requiring amputation. Amputation was needed in three other patients with technical failure, while a further patient had a successful repeat subintimal angioplasty.

Conclusion: Subintimal angioplasty has an increasing role in limb salvage, particularly in patients unfit for operation.

Outcome of subintimal angioplasty in a district general hospital

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Background: The results from major institutions of subintimal angioplasty are good. The aim was to determine the early and intermediate outcome of the technique of subintimal angioplasty in a district general hospital.

Methods: After formal training, two consultant radiologists performed subintimal angioplasty on 50 consecutive patients for the treatment of intermittent claudication (23 patients) and ulceration or gangrene (27). Patients were classified as Rutherford grade III–VI. The patient group contained 35 men and 15 women with a median age of 72 (range 45–93) years. The median treated length was 17·5 cm in the superficial femoral artery, 12·5 cm in the popliteal artery and 7·5 cm in the peroneal artery. Those with a technically successful procedure were followed with clinical assessment at 6 weeks and colour duplex ultrasonography at 6 months.

Results: Thirty-nine (78 per cent) of the 50 procedures were technically successful. Sixty per cent of these were patent at 6 months on colour duplex ultrasonography. The primary technical success rate in the first 25 consecutive patients to undergo angioplasty was 64 per cent (16 patients), compared with 92 per cent (23 patients) in the second group of 25; this difference was significant ($P = 0\cdot004$, χ^2 test). The overall patency rate at 6 months in the first 25 consecutive patients was 43 per cent, compared with 69 per cent in the second 25; this difference was statistically significant ($P = 0\cdot02$, χ^2 test).

Conclusion: After a short learning interval, subintimal angioplasty can be used effectively in a district general hospital, with good medium-term patency rates.

Midterm results of a single endovascular device for repair of an abdominal aortic aneurysm: one centre's experience of the Vanguard device

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Background: The aim of the study was to evaluate the midterm results of the Vanguard device.

Methods: All deployments performed in a single centre with follow-up according to EUROSTAR criteria were reviewed.

Results: Fifty-five patients underwent deployment of a Vanguard device between December 1995 and July 1999. All stents were implanted successfully, with a perioperative mortality rate of 5 per cent (three of 55 patients). Twelve systemic complications (23 per cent) and three access site complications (6 per cent) were observed. Predischarge computed tomograms revealed one type I and five type II endoleaks. Eleven patients died during follow-up (median 23·4 (range 6–48) months) (ten unrelated, one ruptured abdominal aortic aneurysm). The 2-year survival rate was 70 per cent. Eleven occluded graft limbs (22 per cent; median onset 18 months (range from 24 h to 36 months)), one graft migration and eight late endoleaks (16 per cent; median onset 24 (range 3–42) months) were observed. The 2-year intervention-free survival rate was 68 per cent, with an endoleak-free survival rate of 84 per cent. Median (range) neck diameter increased from 20 (15–23) to 23 (17–27) mm at 24 months ($P < 0\cdot01$).

Conclusion: The onset of late endoleak and limb occlusion suggests that follow-up is essential, even after 36 months. The increasing neck diameter may prove significant with regard to long-term fixation of the proximal device.

Thoracic stent grafts

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Background: The Endovascular Aneurysm Repair trial of infrarenal aortic aneurysm repair requires 20 operations to be performed at each centre to eliminate learning curve errors. An analysis was undertaken of the authors' learning curve experience of commercially made thoracic stent grafts.

Methods: Stent grafting was attempted in 26 patients. Aortic pathology included 13 atheromatous aneurysms, six dissections, one coarctation, three false aneurysms and three transections. Successful deployment was performed in 24 patients (92 per cent), but failed in two women due to small iliac arteries. Stent grafts used were Gore Excluder (16 patients), AneuRx (six), Vanguard (one) and Stenford (one). Four patients required two stents, two needed three stents, and 18 had a single stent.

Results: Thirteen elective procedures were uneventful. Two deaths occurred in 11 urgent procedures, from pulmonary embolism and aortic rupture of an unsuspected false aneurysm. The overall in-hospital mortality rate was 8 per cent (two of 24 patients). One graft with a persistent endoleak was removed at open repair at 6 weeks. The subclavian artery origin was covered in three elderly patients, resulting in minor distal ischaemia. No spinal cord problems were seen. One patient died from pneumonia at 8 weeks, and another died from rupture at 28 months as a result of prolapse of the stent into the aneurysm sac.

Conclusion: Assessment of the diameter of the iliac arteries is important, especially in women, to ensure that they accommodate the size of the sheath. Patients with false aneurysms have a poor outcome, and treatment by stent grafting may not be durable. Covering the origin of the left subclavian artery can be undertaken in elderly patients with transient minor symptoms. The use of stent grafts in acute type B dissection should be the subject of a randomized trial. Continued surveillance is essential.

Radiological intervention to the iliac segments for patients with claudication and coexistent significant infrainguinal disease

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Background: The policy with regard to patients with lifestyle-limiting intermittent claudication is to investigate with duplex ultrasonography and then to treat suitable lesions in the aortoiliac system with balloon angioplasty with or without stenting. In those with coexistent infrainguinal disease, further management is conservative. The aim of this study was to assess the outcome of iliac intervention in this group of patients.

Methods: Over 30 months 600 patients with intermittent claudication were assessed; 110 subsequently underwent balloon angioplasty (87 aortoiliac and 23 infrainguinal). Of those undergoing aortoiliac angioplasty 47 also had significant infrainguinal disease. These 47 had a median claudication distance of 80 m and median maximum walking distance 180 m. They underwent angioplasty of 61 arterial segments (one aorta, 32 common iliac, 28 external iliac), with 11 stents deployed in eight patients. There were no immediate complications and a technically satisfactory result was obtained in all but one patient. All patients were reassessed at 6 weeks.

Results: The *Table* gives the findings at 6 weeks.

	No change	Improved (20–99%)	Improved (≥ 100%)
Claudication distance (m)	5 (11)	9 (19)	33 (70)
Maximum walking distance (m)	9 (19)	19 (40)	19 (40)

Values are median with percentages in parentheses

Fifteen patients (32 per cent) had a pain-free walking distance greater than 450 m and a further two were limited by angina rather than claudication. Overall the 47 patients had a median claudication distance of 270 m and median maximum walking distance of 420 m.

Conclusion: Even in the presence of significant infrainguinal disease, angioplasty in the aortoiliac segments at least doubles the claudication distance in 70 per cent of patients, and appears to be safe. Radiological intervention in these patients is worthwhile.

Outcome analysis of over 1000 episodes of limb ischaemia treated by peripheral thrombolysis

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Background: In the past 10 years, 13 hospitals with an interest in peripheral arterial thrombolysis have collected information on 1064 episodes of thrombolysis used to treat some 933 patients. The aim of the database was to identify clinical factors at the time of admission to hospital and relate them to the patients' outcome.

Methods: After verification of the database, a regression analysis was done in three stages: univariate analysis, logistic regression including the initial success of thrombolysis, and logistic regression analysis excluding initial success. The endpoints were amputation-free survival (AFS), survival but with amputation, and death. Statistical analysis was performed with SPSS software (SPSS, Chicago, Illinois, USA).

Results: The overall AFS was 72·9 per cent; 12·6 per cent of events resulted in amputation and 12·9 per cent of patients died. Univariate analysis showed that patients receiving warfarin had a survival advantage, whereas those with diabetes and ischaemia that caused sensory loss were significantly more likely to require amputation. Logistic regression analysis confirmed the above effects of diabetes and ischaemia. Major haemorrhage occurred in 8 per cent of events, but there was a significantly increased risk if the patient had a history of peripheral vascular disease ($P = 0{\cdot}007$) or presented with graft thrombosis ($P = 0{\cdot}001$). Stroke occurred in 2·4 per cent of events; a greater incidence occurred in patients with a duration of ischaemia of less than 8 h.

Conclusion: Further detailed analysis of this large and unique database should help clinicians to refine the indications for peripheral thrombolysis in the management of acute leg ischaemia.

Treatment of the hostile groin: 5-year follow-up of the obturator foramen bypass

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Background: Infection in the groin threatens both life and limb. In recent times virulent organisms, especially methicillin-resistant staphylococci, have proved difficult to treat. The obturator foramen bypass, although performed infrequently, represents an extra-anatomical solution to the 'hostile groin'. The aim of the study was to examine the primary and secondary graft patency rates in 26 patients (28 procedures) performed in one hospital over 10 years.

Methods: There were 17 men and nine women with mean age of 65 (range 49–78) years. All procedures except one were performed with expanded polytetrafluoroethylene (6 mm in 24 patients; 8 mm in three). Twenty-one patients had critical ischaemia with rest pain or tissue loss. The inflow vessel was the common iliac artery in 25 patients and the lower abdominal aorta in three. The distal anastomosis was to the profunda in two grafts, to the suprageniculate popliteal artery in 24 grafts and to the infrageniculate popliteal in two.

Results: Patency rates were calculated with the Kaplan–Meier life-table method.

	Primary patency	Secondary patency
Time after operation (years)		
1	21	23
2	12	14
5	5	

There were nine primary failures (five in the first year and the remaining four between 2 and 5 years). All failed bypasses were re-explored. Three of nine bypasses required intraoperative angioplasty of the inflow, and one graft had angioplasty of the distal anastomosis. Six patients eventually had amputations, four above knee and two below knee, one of whom had a patent graft.

Conclusion: The obturator foramen bypass, although technically demanding, is a viable solution in the individual with groin sepsis and ischaemia. Frequently these patients have good calibre vessels above and below the problem groin.

Pharmacotherapy and outcome in intermittent claudication

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Background: Intermittent claudication (IC) carries an increased risk of vascular death compared with that in age-matched controls. The role of antiplatelets and statins in the reduction of this risk in new claudicants was evaluated in an observational study of a prospectively gathered database, the General Practice Research Database (GPRD), with 430 practices contributing 8 million patients in the UK.

Methods: All patients aged 40–79 years with newly diagnosed IC and no history of previous peripheral vascular disease were identified using recognized GPRD OXMIS codes. Prescription of antiplatelet therapy (APT) up to 12 months before or after diagnosis, and the use of statin therapy (ST) at the time of diagnosis, of IC was noted. Odds ratios (ORs) adjusted for APT, ST, sex, age, smoking, diabetes, and coexisting cardiac and cerebrovascular disease were calculated. Patients with critical limb ischaemia were excluded. Outcome measures were all-cause death, fatal stroke and fatal myocardial infarction (MI) up to 5 years after diagnosis of IC.

Results: Between 1988 and 1993, 20 474 patients with newly diagnosed IC were identified. The *Table* summarizes the results.

Conclusion: Prescription rates of statins and antiplatelets in new claudicants in the UK are low and could be improved. These results suggest that ST is associated with a significant reduction in all-cause mortality rate in new claudicants. Patients receiving APT demonstrated a significant reduction in death from MI.

Table Pharmacotherapy and outcome in intermittent claudication, P. F. S. Chong, H. Seaman, J. Golledge, R. Gibbs, R. Lawrenson, R. M. Greenhalgh and A. H. Davies

	APT	No APT	Adjusted OR for APT*	ST	No ST	Adjusted OR for ST*	Combined APT + ST
Total patients	7652 (37·4)	12 822 (62·6)		498 (2·4)	19 976 (97·6)		340 (1·7)
Fatal MI	233 (3·0)	300 (2·3)	0·53 (0·42–0·69)†	6 (1·2)	527 (2·6)	0·69 (0·26–1·86)	2 (0·6)
Fatal stroke	181 (2·4)	181 (1·4)	0·79 (0·62–1·01)	2 (0·4)	360 (1·8)	0·37 (0·08–1·66)	2 (0·6)
All deaths	1210 (15·8)	1 720 (13·4)	0·94 (0·87–1·03)	23 (4·6)	2 907 (14·6)	0·29 (0·19–0·45)†	15 (4·4)

Values in parentheses are percentages or *95 per cent confidence intervals. †$P < 0{\cdot}05$

Impact of angioplasty on infrainguinal bypass for critical ischaemia of the leg

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Background: Both angioplasty and infrainguinal bypass procedures may be used to achieve limb salvage in patients with critical ischaemia. The authors investigated the effect of the introduction of angioplasty on the frequency with which infrainguinal bypass was performed and, second, the changes in outcome of infrainguinal bypass following the introduction of angioplasty.

Methods: All patients had critical ischaemia of the leg. Three patient groups were studied: 215 patients undergoing infrainguinal bypass before the introduction of angioplasty (1986–1991), 216 patients who had infrainguinal bypass after the introduction of angioplasty (1993–1998) and 193 patients undergoing angioplasty in the same 5-year interval (1993–1998).

Results: The age and risk profile of the three groups was identical. The overall caseload increased by 19 per cent following the introduction of angioplasty. Primary and secondary patency rates were superior for bypass compared with angioplasty, but were similar for the two bypass groups (5-year primary patency rate 60 per cent *versus* 18-month primary patency rate 45 per cent; 5-year secondary patency rate 80 per cent *versus* 18-month secondary patency rate 60 per cent). By 18 months 26 per cent of patients having angioplasty had gone on to have bypass. The limb salvage rate of 90 per cent at 1 year was similar for all groups. Survival was significantly higher in the group of patients undergoing bypass from 1993 to 1998 compared with the other two groups (80 *versus* 60 per cent; $P < 0 \cdot 0002$).

Conclusion: The introduction of angioplasty has increased overall workload. Angioplasty has a lower patency rate than bypass but a comparable limb salvage rate, making it a suitable alternative to bypass in the management of patients with critical ischaemia.

Prospective audit of major amputations for peripheral vascular disease

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Background: Primary amputation followed by prosthetic fitting has been proposed as an alternative worth considering if lower limb bypass has poor prospects of patency. This is an outcome audit of major amputations at a single centre where amputations were performed only if limb salvage was not possible.

Methods: Consecutive major amputations ($n = 162$) for peripheral vascular disease from January 1996 to December 1998 were studied prospectively. Duration of hospital stay, causes of morbidity and mortality, and reasons for being unsuitable for prosthesis were recorded. Mobility at admission and after rehabilitation was documented using a standard grading system (grades 1–6).

Results: There were 114 above-knee, 45 below-knee and three through-knee amputations. The 30-day mortality rate was 14 per cent (22 patients), increasing to 29 per cent (47) at 9 months. Some 57 patients (35 per cent) were rehabilitated with a prosthetic limb (30 above knee, 27 below knee). Mobility with prosthesis was better or maintained in 24 patients, worse by one grade in 17, and by two or more grades in the remaining 16. Fifty-eight patients (36 per cent) were unsuitable for an artificial limb; in four this was because of stump-related problems, and the rest because of co-morbidity. Cardiorespiratory events were the most frequent cause of morbidity and mortality. The mean hospital stay after amputation was 37 days in survivors.

Conclusion: Perioperative and late mortality rates following amputation are high. A large proportion of amputees were not suitable for prosthesis, mainly because of co-morbidity. Of the patients receiving a prosthesis, only 42 per cent (15 per cent of the total) maintained or improved their mobility. The results are unlikely to be different if a policy of selective primary amputation were to be adopted. The outcome of amputation is worse than widely perceived despite the improvements in prostheses and a well executed rehabilitation process.

Interhospital provision of emergency vascular services for a large population: early outcomes and clinical results

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Background: In 1999 an emergency vascular service for Bristol and Avon (including Weston-Super-Mare) (population approximately 1 million) was initiated.

Methods: Collaboration between Bristol Royal Infirmary, Frenchay and Southmead Hospitals provides week-on–week-off vascular cover for patients requiring urgent and emergency interventions within 24 h. The rota accommodates National Confidential Enquiry into Perioperative Deaths and Vascular Surgical Society of Great Britain and Ireland recommendations, governance issues, and enhances emergency vascular care for Avon residents. Prospectively collected data for the first year (May 1999 to April 2000) are reviewed.

Results: There were 289 emergency admissions. (In-hospital referrals were not transferred but contributed up to 40 per cent of the extra emergency workload per unit.) Referrals were also accepted from seven Trusts outside the designated catchment area. Caseload included 86 patients with a ruptured or acutely symptomatic aortic aneurysm, of whom 69 underwent operation (30 per cent mortality rate); 17 patients were not operated

on. Some 136 patients had critical leg ischaemia (43 acute, 93 chronic); angiography or duplex ultrasonography was performed in 105 cases (77 per cent); 39 patients (29 per cent) had undergone previous intervention for peripheral vascular disease; the mortality rate was 18 (13 per cent) of 136; 18 (13 per cent) of 136 patients required an amputation. Other cases included: upper limb ischaemia, 20 (7 per cent); paediatric emergency, seven (2 per cent); symptomatic carotid disease, five (2 per cent; four endarterectomies with no death or stroke). Some 5 per cent of referrals were inappropriate (venous ulcer, spinal stenosis, etc.). No outcomes were compromised by interhospital transfers. Vascular surgeons operated on nine high-risk patients away from their 'base' hospital. A consultant was the principal or assistant operator in more than 95 per cent of operations but, despite trainee rota adjustments, a designated vascular trainee was present in only about 40 per cent of cases.
Conclusion: Interhospital provision of emergency vascular services for a large population is feasible, does not compromise quality of care, and regulates emergency workload. Further attention to training issues is indicated.

P-POSSUM models for abdominal aortic aneurysm surgery

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Background and methods: POSSUM (Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity) data on 444 (213 emergency, 231 elective) admissions for abdominal aortic aneurysm (AAA) surgery between August 1993 and July 2000 were analysed using the P-POSSUM equation for general surgery and the P-POSSUM equations developed for the Vascular Surgical Society of Great Britain and Ireland (physiological and operative and physiology only).
Results: All three equations successfully modelled the elective admissions but failed to fit the emergency admissions and the elective and emergency admissions combined. This suggests that admission method (not a POSSUM data item) is an important factor for patients with AAA. However, with these data it was not possible to generate a model, including admission method, that successfully modelled the combined elective and emergency data. Emergency AAAs had to be treated separately. The 213 emergency admissions were divided into two groups by operation date. The first 106 (training set) were used to form logistic regression models following the P-POSSUM methodology. These models were found successfully to fit the remaining 107 records (test set) on prospective application, as shown in the *Table*.

Risk range	Mean risk	No. of operations	Predicted deaths	Reported deaths	χ^2
>0, ≤30	23·58	24	6	8	1·27
>30, ≤45	37·89	45	17	16	0·10
>45, ≤60	51·45	23	12	8	2·56
>60, ≤100	68·99	15	10	9	0·57
>0, ≤100	41·95	107	45	41	4·50

Critical value = 9·49, $\chi^2 = 4{\cdot}50$, 4 d.f., $P = 0{\cdot}34$; no evidence of lack of fit

Conclusion: Emergency AAAs appear to be fundamentally different from elective AAAs and other vascular cases, and require their own distinct risk model. The ability to model risk for elective AAAs using a physiology-only risk model could perhaps be used to optimize the timing of operation as well as informing all concerned of the risks involved.

Poor outcome following revascularization predicted by thromboelastography

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Background: Infrainguinal revascularization procedures are associated with a high risk of graft failure, amputation and early death. Hypercoagulability predicts a poor overall outcome but conventional tests are expensive and results are not immediately available. A cheap, rapid method for identifying hypercoagulability would allow screening before revascularization. Thromboelastography (TEG) is a rapid, reliable, bedside method of assessing whole blood clotting. Normally used to assess hypocoagulability, this study determined the role of TEG in identifying patients with a poor prognosis following revascularization.
Methods: Between November 1998 and January 2000, 106 patients with critical leg ischaemia were admitted for radiological or surgical revascularization (mean age 71 (range 33–90) years). All underwent TEG analysis, standard thrombophilia screening (STS), and fasting homocysteine and fibrinogen assays. All patients were followed for 6 months after revascularization by means of clinical examination, ankle : brachial pressure index (ABPI) and duplex imaging.
Results: At the 6-month follow-up of 106 patients, 29 (27 per cent) had arterial or graft occlusion, five (5 per cent) had died and four (4 per cent) had undergone a major amputation. Analysis of risk factors revealed that a hypercoagulable TEG ($P = 0{\cdot}0009$), STS and/or raised fibrinogen level ($P = 0{\cdot}01$), and rest pain ($P = 0{\cdot}006$) were associated with poor outcome. Other factors such as age, sex, diabetes, current or previous smoking, coronary artery or cerebrovascular disease, hypertension, previous intervention, aspirin or lipid-lowering therapy were not significantly different. In addition, hyperlipidaemia, hyperhomocysteinaemia, raised level of C-reactive protein, eyrthrocyte sedimentation rate, lipoprotein a level, haemocrit,

STS or fibrinogen alone were not useful as predictors of poor outcome.

Conclusion: TEG, a rapid inexpensive test of hypercoagulability, is associated with poor outcome following infrainguinal revascularization.

Risk modelling for carotid endarterectomy

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Background: A 30-day stroke or death rate of 3–10 per cent has been reported in patients undergoing carotid endarterectomy (CEA). The aim of this study was to identify the risk factors that influenced the outcome and to develop a logistic regression model that can aid in the comparative audit of CEA.

Methods: Some 836 CEAs performed by four vascular surgeons from 1992 to 1999 were analysed. The median age of the population was 69 (range 38–86) years, and the male : female ratio was 1·6. Multiple logistic regression was used to model the effect of 15 risk factors on the 30-day stroke and death rate. The outcome after risk adjustment was compared for four surgeons and two vascular units.

Results: The overall 30-day stroke and death rate was 3·9 per cent. Regression modelling identified heart disease, diabetes and stroke at presentation as significant risk factors. A risk score of 1 was assigned to each of these risk factors to produce a logistic regression equation (where P is the probability of 30-day stroke or death):

$$\ln(P/1 - P) = 0{\cdot}9294(\text{risk score}) - 4{\cdot}2726$$

Risk score	30-day stroke or death risk (%)
0	1·4 (0·9–2·1)
1	3·4 (2·2–5·2)
2	8·3 (2·9–21·5)
3	18·8 (3·5–58·8)

Values in parentheses are 95 per cent confidence intervals

The observed 30-day stroke and death rate for four vascular surgeons was 3·0, 4·0, 4·2 and 4·3, and for two vascular units was 3·9 and 3·9. Differences between the surgeons and the vascular units were not statistically significant after allowing for risk adjustment using this model.

Conclusion: Multiple logistic regression models can successfully identify patients at higher risk from CEA, and aid in the comparative audit of surgeons and vascular units.

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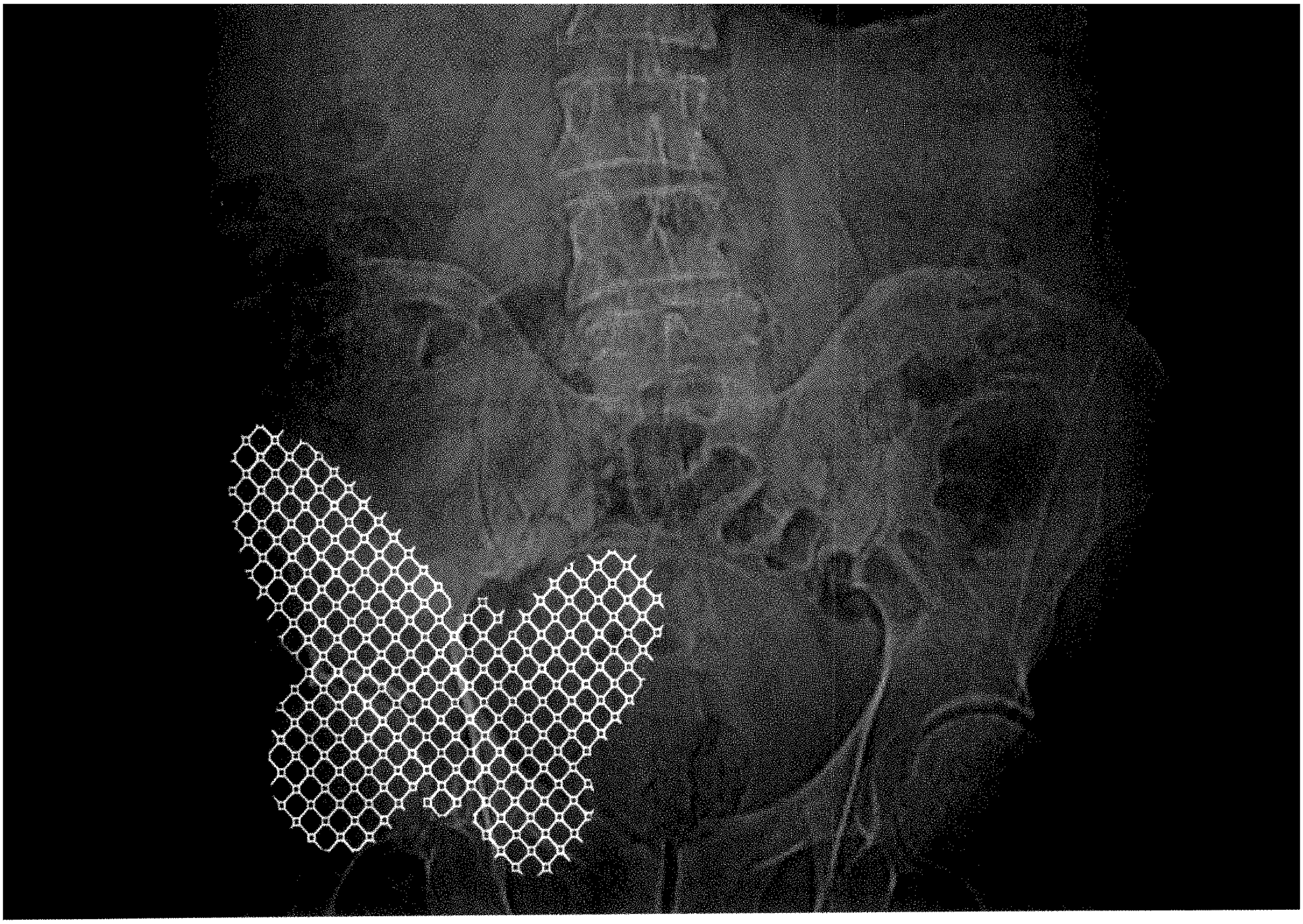

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The *BJS* ISSN 0007-1323

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Typeset and printed by Information Press Ltd, Oxford

*Periodicals postage is paid at Rahway, NJ and Additional Mailing offices. Postmaster: send address corrections to. *BJS*, c/o Mercury Airfreight International Ltd, 365 Blair Road, Avenel, NJ 07001, USA

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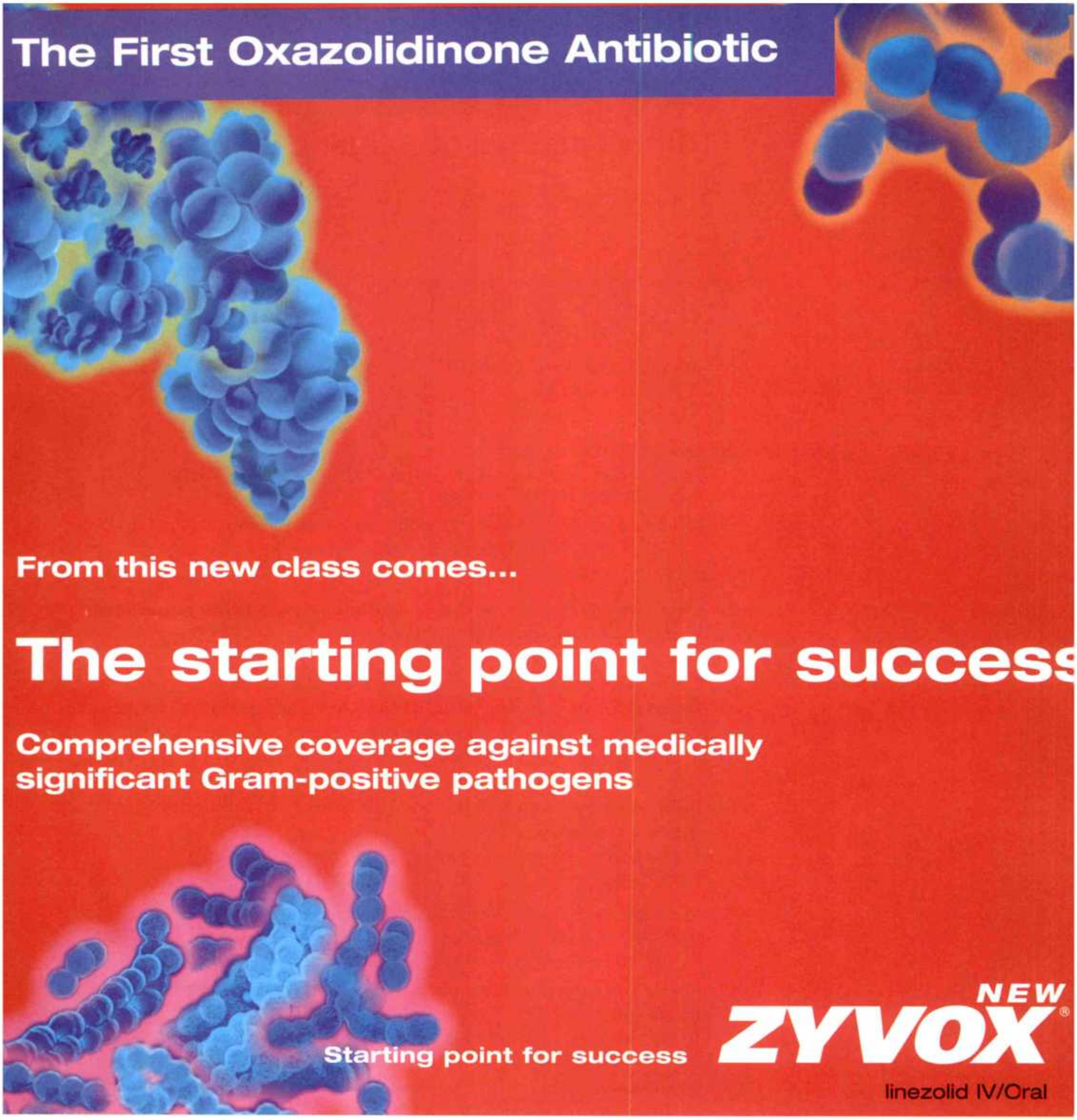
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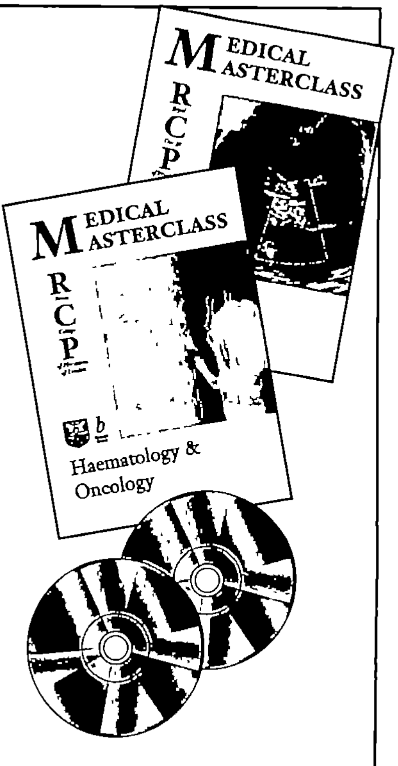
0007-1323(200105)88:5;1-V



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Leading article

Screening for abdominal aortic aneurysm

J. S. Lindholt

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Despite increased numbers of elective operations for abdominal aortic aneurysm (AAA), the sex- and age-standardized mortality rate of ruptured AAA continues to increase. The lethality of ruptured AAA continues to be 80–95 per cent[1], compared with 5–7 per cent for elective surgery for symptom-free aneurysm. An asymptomatic phase with a relatively low-risk treatment, compared with the symptomatic phase, is a good starting point for considering screening. However, there are several World Health Organization (WHO) criteria[2] for screening that must be fulfilled before it can become a reality.

First, it is widely acknowledged that ultrasonography is a suitable method of screening. Patient acceptance rates of 53–79 per cent have been achieved[1]. Furthermore, those persons at highest risk of having an AAA attend screening more often than those at low risk, and diseases affecting mobility are not associated with non-attendance[3,4]. The infrarenal aorta can be visualized in 98–100 per cent of cases, but the exact sensitivity and specificity of such screening is unknown. Nevertheless, by using the inter-observer variation and the distribution of the observed aortic diameter, the sensitivity and specificity have been estimated as 98 and 99 per cent respectively[5]. The usual problems of false-positive and -negative findings seem negligible because such errors are inevitably revealed at follow-up of small AAAs or by repeated (interval) screening[1,5,6].

Interval screening is needed because the prevalence of AAA increases with age and some of the newly recognized aneurysms will be suitable for surgery[6], but the amount of screening must be minimized because of its associated psychological and economic costs[1,7,8]. The Viborg study[6] showed that 97 per cent of the interval cases developed from aortas that initially measured 2·5–2·9 cm. The remaining 3 per cent developed from aortas initially measuring less than 2·5 cm, but these aneurysms were all below 3·5 cm and so would probably never become clinically relevant. Rescreening in the Viborg study[6] and in the Aneurysm Detection and Management (ADAM) study[9] showed that none of the newly found aneurysms was more than 5 cm in diameter after 4–5 years. Consequently, rescreening could usefully be restricted to aortas initially measuring 2·5–2·9 cm, i.e. approximately 5 per cent of the screened population, at intervals of 5 years.

There is a risk that screening may lead to disproportionate fear and stigmatization, with loss of quality of life. Consequently, one of the WHO criteria for screening is that the disease screened for must be a major health problem[2]. Today 1–3 per cent of all deaths in men aged 65–80 years are caused by AAA; some might question whether or not this represents a major health problem. Certainly the offer of screening for aneurysm is known to cause a transient mild fearful reaction[7] and it is fortunate that repeat screening is only required in 5 per cent of those with initially negative findings[6].

Another consideration is that the indications for treatment must be clear[2]. The size of an AAA is the only widely accepted prognostic indicator of rupture. The UK Small Aneurysm Trial[10] and the similar ADAM study (unpublished data) in the USA each randomized over 1000 4·0–5·5-cm aneurysms to early surgery or watchful waiting. No differences in AAA-related mortality rate were noted between the two arms of the studies after 5 years. However, because of the known strong correlation between AAA size and risk of rupture, the smallest aneurysms in the studies must move the conclusion towards watchful waiting and the largest towards early surgery. The optimal discriminating size between waiting and early surgery probably lies in the upper half of the studied size interval. However, no matter what discriminating point is chosen, AAAs will still rupture during conservative treatment and patients will still die after surgery for a lesion that would never have ruptured. This ethical problem is serious but insoluble.

Treatment must be acceptable[2]. Survivors of surgery have the same quality of life as the general population of the same age[7], and it seems that only 2–5 per cent of patients refuse the offer of surgery[1]. However, at least 10 per cent of those with sizeable aneurysms have contraindications to surgery and 85–90 per cent of the lesions diagnosed at screening are initially too small for operation[1]. Follow-up without surgery decreases quality of life[7,10]; still, half of these patients will undergo surgery within 5 years, and there is the possibility of developing models to predict cases for operation, based on serological markers with an acceptably high sensitivity and specificity. Efficient anti-inflammatory or antibiotic treatment is another possibility. Such developments might reduce the psychological side-effects of knowing that one has an aneurysm, but at present optimal follow-up is the only way of doing this[6]. AAAs of 3·0–3·5 cm diameter require follow-up only at intervals of 3 years, 3·5–4·0-cm AAAs every other year, and those over 4·0 cm yearly[6].

Finally, the benefits of screening must outweigh the costs[2]. The only randomized clinical trial of screening for AAA showed that it produced a 50 per cent reduction in the aneurysm-related mortality rate[11]. The costs and benefits of screening are currently being evaluated in randomized clinical trials in the UK, Australia and Denmark, involving over 100 000 65–79-year-old men. These studies are expected to answer the final points[2]: the ethical dilemma of the prophylactic operation, limited adverse psychological side-effects and minor uncertainties about the indications for treatment seem not to outweigh the benefits of screening if overall cost proves attractive. It is interesting to speculate, however, whether or not the forthcoming national results will be generalizable to other countries. Aneurysm-associated and overall mortality rates, motivation for screening, transport opportunities, alertness for AAA, and cost of diagnosis and treatment no doubt differ from nation to nation, with corresponding differences in cost and benefit balances.

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Clinical dilemma

An unexpected liver secondary

At operation for carcinoma of the rectum an unexpected metastatic tumour deposit is found in the liver. What is the most appropriate surgical approach? Professors Balladur and Parc of Paris, France, reply.

Surgery is the treatment of choice for operable metastatic colon cancer confined to the liver, with a 5-year survival rate of 20–40 per cent. In experienced hands the operative mortality rate is less than 5 per cent and the morbidity rate is of the order of 20 per cent. Approximately 15–20 per cent of patients will have liver metastases at the time of diagnosis of the primary colorectal tumour. When the liver metastases are resectable the surgeon must decide between a one-stage or two-stage procedure.

In the context of the present Dilemma, three main points need to be addressed.

1 Is there an oncological advantage in resecting the primary and hepatic metastasis in one stage?
2 Does a one-stage procedure influence the operative risk?
3 Is resection of a rectal cancer compatible with simultaneous hepatic resection?

First, from an oncological point of view, given the immunosuppression noted after major surgery it is tempting to conclude that a one-stage procedure diminishes the risk of rapid tumour growth. There is, however, no evidence in the literature to support this hypothesis. Conversely, combining hepatic resection with rectal resection may increase the need for peroperative or postoperative blood transfusion, which is itself known to be associated with an immmunosuppressive effect. Scheele *et al.*[1] reported a 5-year survival of 30 per cent for 90 patients undergoing a one-stage procedure, no different to that of 42 patients undergoing a two-stage procedure. In a series of 36 patients reported by Vogt *et al.*[2] the overall 5-year survival rate was 20 per cent in both groups.

Resection of a liver lesion at the time of rectal surgery may well be inappropriate for an individual patient. A delay of 2–3 months allows further liver imaging (computed tomographic portography has a high sensitivity for lesions of less than 1 cm in diameter) and the exclusion of pulmonary metastases. The delay also allows some patient 'self selection', multiple undetected metastases becoming manifest indicating a group of patients in whom liver surgery would be of no benefit. For other patients there is no evidence that such a delay decreases the chance of long-term survival; the authors use this period to offer chemotherapy.

A second consideration is a possible influence on morbidity and mortality rates. In a retrospective report from the French Association of Surgeons[3] involving more than 2000 patients, the operative mortality rate was 6·1 per cent after a one-stage procedure involving a major hepatectomy (more than two segments) compared with 2·4 per cent after a two-stage procedure. However, no difference was observed for minor hepatectomies (two or fewer segments). In a series reported by Elias *et al.*[4] 53 patients underwent simultaneous hepatectomy and intestinal anastomosis. There was no operative death and the morbidity rate was 19 per cent, 4 per cent related to the intestinal anastomosis. In a series of 90 patients undergoing simultaneous resection reported by Scheele *et al.*[5], there was a postoperative morbidity rate of 22 per cent, with 14 per cent related to the anastomosis; there were 13 anastomotic leaks.

The authors perform the intestinal anastomosis before embarking on any hepatic surgery; clamping of the hepatic pedicle may cause some oedema of the intestinal wall, but this does not impair anastomotic integrity in any way. Conversely, portal hypertension, induced by hepatic pedicle clamping and by hepatectomy, may in itself render the construction of an anastomosis more difficult. Some authors have proposed intermittent clamping to safeguard intestinal healing[4]. In the present authors' view the improvement in methods of liver transection allows minor resections to be performed without hepatic pedicle clamping. At the same time there is no evidence that impairment in liver function noted after major hepatic surgery compromises intestinal healing. In the series reported by Elias *et al.*[4] 11 patients underwent resection of over 50 per cent of the liver mass with no anastomotic complications.

It seems unlikely that opening the bowel increases the likelihood of infective complications related to the cut liver surface, nor does hepatic resection impair intestinal healing. To minimize any possible risk, bowel preparation must be scrupulous, the colorectal surgery should be performed before the liver surgery, and there should be a complete change of instruments between the two stages.

Is resection of the rectal cancer compatible with hepatic resection? In the series by Scheele *et al.*[5] the two anastomotic leaks directly responsible for death occurred in patients who had undergone a low colorectal anastomosis. The authors treat all low colorectal or coloanal anastomoses as high risk and, as such, they should not be associated with major hepatic resection.

From a technical point of view, discovery of a metastatic lesion by palpation at the time of anterior resection requires a histological diagnosis before embarking on further treatment; it also suggests the need for intraoperative ultrasonography to visualize the rest of the liver. False negatives are less than 2 per cent in experienced hands.

Searching the literature to answer the question about how to proceed in this clinical situation yields little in the way of hard data, but obviously a prospective randomized trial would be difficult or impossible to perform. The available evidence suggests that:

1 There is no significant advantage in a one-stage procedure from an oncological point of view.
2 The perioperative mortality rate is higher when a major hepatic resection is performed.
3 For anterior resection of the rectum, the risk of anastomotic leakage is increased if simultaneous hepatectomy is also performed.

When a hepatic metastasis is discovered at the time of an anterior resection, in addition to the above points the operating surgeon must also consider:

1 The completeness of the preoperative staging investigations.
2 The local experience in peroperative ultrasonography.
3 The completeness of preoperative patient counselling and consent.

The authors' approach is to resect small solitary hepatic metastases as long as this involves only a minor hepatic resection, a margin of at least 1 cm is assured, and this requires only minimal modification to the incision.

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Review

Oesophageal diverticula

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Background: Oesophageal pulsion diverticula, excluding pharyngeal types, are uncommon sequelae of oesophageal dysmotility. Current opinion favours myotomy as effective therapy, but the role of diverticulectomy, myotomy selection and placement, and the need for fundoplication remain unresolved.

Methods: A Medline search and review of references identified relevant English language articles. Data on epidemiology, aetiology, oesophageal motility, pathology, symptomatology, investigations, surgical management and outcome were examined.

Results: Data were largely retrospective. Significant morbidity and mortality were associated with pulmonary aspiration and diverticulectomy site leaks. Surgical outcome was similar whether or not a diverticulectomy was added to a myotomy, but a myotomy clearly reduced the risk of leaks. Fundoplication reduced the incidence of postcardiomyotomy reflux symptoms. Results from minimally invasive techniques were similar to those of open surgery.

Conclusion: Surgery should be reserved for symptomatic patients; asymptomatic patients may benefit from surveillance. Pulmonary aspiration mandates surgical intervention. Myotomy remains the mainstay of treatment and an adequate subdiverticular extension is crucial in relieving obstruction. A partial fundoplication is preferred in selected patients. Minimally invasive techniques should become the routine approach for oesophageal pulsion diverticula.

Paper accepted 27 November 2000

British Journal of Surgery 2001, 88, 629–642

Introduction

The literature describes a remarkable and ongoing evolution in the understanding and management of oesophageal diverticula, spanning almost two centuries. Oesophageal diverticula are considered to be rare but this has not deterred interest in the condition, either historically or in the present era. The pathophysiological factors involved are not precisely understood, and the surgical management remains controversial and somewhat confusing. This paper reviews the English language literature on oesophageal pulsion diverticula, excluding the pharyngeal type, to determine a rational surgical approach to the disorder.

Historical considerations

DeGuise (1804) is credited as the first to accurately describe the symptoms associated with an epiphrenic (or lower) oesophageal diverticulum[1–4]. Mondiere (1833) and Rokitansky (1840) proposed traction and pulsion forces as possible mechanisms for the formation of middle and lower oesophageal diverticula[1,5]. Reitzenstein (1898) provided the first radiological confirmation of the lesion, and Clairmont (1921) was the first to operate successfully on the pathology[4]. Since the mid-1800s clinicians consistently noted the frequent association of oesophageal motility disturbances, particularly with epiphrenic diverticula, but failed to recognized an aetiological link between the two. Furthermore, Barrett[6] (1933) dismissed this possibility and the concept was ignored thereafter until the 1960s. The elegant work by Cross[7] in 1968, using oesophageal manometry with cinefluorography, provided objective evidence that oesophageal motility disorders were responsible for both mid-oesophageal and epiphrenic diverticula. The appreciation of the primary role of motility disorders, not only in the formation of oesophageal diverticula but also in symptom production, has led to fundamental changes in the surgical management of this pathology. Whereas simple diverticulectomy was historically the procedure of choice, the preference is now for a myotomy to address the underlying motility problem. Despite this understanding, there is still considerable variation in the surgical treatment of pulsion diverticula. The contentious issues are: (1) Who should undergo surgery? (2) Should myotomy be selective or routine? (3) Where is a myotomy best sited? (4) Is an antireflux procedure necessary? (5) How should the diverticulum be managed? (6) What are the merits of minimal access surgery?

Classification

Oesophageal diverticula are commonly classified according to wall structure, origin, location and mechanism of formation. The location and mechanism of formation are the most relevant surgical features.

Wall structure

A true diverticulum retains all layers of the oesophageal wall. A false one lacks or has an attenuated muscularis propria. The term 'pseudodiverticula' is confusing; it describes diverticula that lack an epithelial lining, intramural sacculations from dilated submucosal glands, the transient appearance of diverticula during incoordinate contractions, and false diverticula as defined above[7–12].

Origin

Oesophageal diverticula are either congenital or acquired lesions. According to the literature adult congenital diverticula are extremely rare and result from incomplete closure of the tracheo-oesophageal common cavity[7], or from oesophageal duplication with heterotopic mucosa[13,14]. Congenital diverticula are usually true diverticula. Most oesophageal diverticula present later in adult life, have a false wall and are acquired.

Location

Proximal oesophageal pulsion diverticula (e.g. Killian–Jamison type) occur rarely[9,15] and may be associated with progressive systemic sclerosis[16,17]. The more typical sites are the mid-oesophageal and epiphrenic regions. The mid-oesophageal or parabronchial segment is defined as 5 cm above and below the level of the carina[9,18]. The epiphrenic region is more variably defined but is generally accepted as the distal 10 cm of the oesophagus[19]. Earlier papers ascribe the most common location to be mid-oesophageal, and diverticula were almost exclusively traction in origin[13,20–23]. Later reports have established that diverticula generally develop in the epiphrenic region and are invariably pulsion in origin[1,5].

Mechanisms of formation

Acquired diverticula are secondary to traction or pulsion forces. Whether both mechanisms may occasionally coexist remains a matter of speculation[6,7]. Perioesophageal adhesions from diseased bronchial lymph nodes lead to typically small, suspended, conical and broad-based, true traction diverticula. The classic cause is pulmonary tuberculosis[18], although anthracosis, histoplasmosis and treated non-Hodgkin's lymphoma have also been reported[24,25]. The pathophysiological mechanisms leading to pulsion diverticula are more complex and are thought to include disordered oesophageal motility, functional or mechanical oesophageal obstruction, and focal weakness of the oesophageal wall[4,5,7,20,26–31]. Under these conditions sufficient pulsion forces may lead to mucosal herniation in the segment of maximum luminal pressure and least wall resistance.

The majority of oesophageal diverticula are acquired, epiphrenic, pulsion diverticula of the false type.

Epidemiology and aetiology

Epidemiology

The reports of oesophageal pulsion diverticula in the literature allude to an uncommon anomaly; the true prevalence remains unknown. Only 129 cases had been published up to 1952[32]. The Mayo Clinic has the largest published collective number of patients with epiphrenic pulsion diverticula in the literature at 450 cases[1,6,26,28,33–35]. Wheeler[36] calculated the prevalence to be 0·015 per cent for epiphrenic diverticula based on radiological appearances in over 20 000 contrast oesophagograms. The estimated prevalence from Japanese series is higher (0·22–0·77 per cent)[37] and may reflect a national screening policy for gastrointestinal cancers. European studies[38,39] have reported similar or higher radiological prevalences of 0·74 and 2 per cent. In addition, oesophageal diverticula are recognized in less than 1 per cent of all oesophagoscopies and occur in 1–3 per cent of patients with dysphagia[9]. The peak age group of those affected is in the sixth and seventh decades of life, with a variable male preponderance in most of the larger series[20,26,28,33,40–43].

Traction *versus* pulsion

In the first half of the previous century tuberculosis was considered the most common cause of oesophageal diverticula[18]. According to detailed postmortem studies by Kragh (1922) tuberculosis-associated lesions were found in 5–6 per cent of autopsies[44–46], but a later postmortem series by Mellins (1952) found only four of 14 traction diverticula from 15 000 autopsies to be related to tuberculosis[18]. The low numbers of mid-oesophageal diverticula in reports since the 1960s parallel the decline in granulomatous diseases involving peribronchial lymph nodes[9,47], and traction diverticula are now considered rare in the western world[18,24,48]. More recently, oesophageal manometry has demonstrated motility disorders in 80–100 per cent of patients with mid-oesophageal diverticula[27,39,44,47]. Since simultaneous manometry and cinefluorography has confirmed the pathogenic role of oesophageal motility disorders in pulsion diverticula[7,27,28,42], it is appropriate to consider all mid-oesophageal and epiphrenic diverticula as pulsion in origin until proven otherwise[27,39,43,44,47].

Motility disorders

The common motility disorders encountered with pulsion diverticula are non-specific oesophageal motility disorder, diffuse oesophageal spasm and achalasia (or cardiospasm) (*Table 1*). Hypertensive lower oesophageal sphincter (HTLOS) and 'nutcracker' oesophagus are diagnosed less frequently. The essential pathophysiological features of these disorders are functional obstruction and high luminal pressures. Most motility disorders inherently involve the distal oesophagus, which may account for the epiphrenic predilection of pulsion diverticula[1,7]. Distal motility and LOS disorders are therefore least likely to cause mid-oesophageal diverticula[44,46]; mid-oesophageal diverticula are more likely to result from diffuse motility disorders[39].

Although achalasia is considered the commonest specific oesophageal motility disorder, less than 5 per cent of those affected develop a pulsion diverticulum[55], presumably because oesophageal contractions are typically hypotensive or absent. The exception is 'vigorous' achalasia, characterized by high-amplitude non-peristaltic contractions that are more likely to generate pulsion forces[51]. Diffuse oesophageal spasm is far less prevalent than achalasia but it results in pulsion diverticula in up to 42 per cent of patients[38,56].

Oesophageal obstruction

Functional obstruction often results from oesophageal dysmotility giving rise to raised luminal pressures.

Table 1 Oesophageal motility disorders associated with pulsion diverticula

			Patients with motility disorder					
Reference	Year	No. of patients	Achalasia	DOS	HTLOS	NSOMD	Unspecified	Total
Studies without manometry								
Vinson[6]	1934	42	8	0	0	0		8 (19)
Harrington[1]	1949	8	4	0	0	0		4 (50)
Allen and Clagett[35]*	1965	160	16	39	0	0		55 (34)
Garcia *et al.*[49]	1972	11	1	8	0	0		9 (82)
Bruggeman and Seaman[20]	1973	80	7	0	4	37		48 (60)
Total		301	36	47	4	37		124 (41)
Studies with manometry								
Kaye[44]	1974	12	1	5	0	6		12 (100)
Debas *et al.*[28]	1980	65	n.s.	n.s.	n.s.	10	40	50 (77)
Rivkin *et al.*[43]	1984	34	0	8	11	15		34 (100)
Fegiz *et al.*[29]	1984	22	2	0	0	10		12 (55)
Evander *et al.*[27]	1986	10	0	2	0	8		10 (100)
Streitz *et al.*[50]	1992	16	5	3	1	1		10 (62)
Fekete and Vonns[41]	1992	27	4	1	0	9		14 (52)
D'Ugo *et al.*[51]	1992	19	4	3	0	7		14 (74)
Altorki *et al.*[52]	1993	20	9	4	1	4		18 (90)
Benacci *et al.*[26]	1993	33	8	3	1	7		19 (58)
Hudspeth *et al.*[53]	1993	9	n.s.	n.s.	n.s.	n.s.	6	6 (67)
Peracchia *et al.*[54]	1994	8	0	0	5	0		5 (62)
Schima *et al.*[39]	1997	30	5	0	0	19		24 (80)
Castrucci *et al.*[40]	1998	51	5	6	12	26		49 (96)
Total		356	43	35	31	122	46	277 (78)
Overall total		657	79 (12)	82 (12)	35 (5)	159 (24)	46 (7)	401 (61)

Values in parentheses are percentage of total number of patients studied. *Includes data of Habein *et al.*[33,34]. DOS, diffuse oesophageal spasm; HTLOS, hypertensive lower oesophageal sphincter; NSOMD, non-specific oesophageal motility disorder; n.s., motility disorder present but not specified

Mechanical obstruction from strictures, webs, tumours and even duodenal obstruction has been associated with oesophageal pulsion diverticula[4,6,26–28,52,57]. This implies that even normal peristaltic contractions against oesophageal obstruction may generate sufficient pulsion forces.

Wall weakness

A pharyngeal diverticulum expands through Killian's dehiscence, an anatomically defined area of least resistance. While it is difficult to demonstrate a comparable morphological arrangement in the oesophagus, many argue for its presence as a pathogenic factor in pulsion diverticula[4,5,20,26,28,29,31]. Inherent weakness may exist where muscularis propria fibres separate in the distal oesophagus[2,58], where vessels and nerves perforate the lateral oesophageal borders[5,59,60], or at the antimesenteric border of the embryonic foregut represented by the right oesophageal wall[61]. Mediastinal structures may limit the appearance of left-sided pulsion diverticula. Injury from reflux oesophagitis with ganglia degeneration may also cause focal weakness[32,45], but the loss of muscle integrity is not a recognized feature of gastro-oesophageal reflux disease (GORD). Perhaps the strongest evidence of the pathogenic role of focal oesophageal weakness comes from reports of iatrogenic pulsion diverticula following localized disruption to the muscularis propria. Oesophageal pulsion diverticula have complicated enucleation of benign tumours[42,61–63], myotomies[37,42,64] and endoscopic perforation[8]. A breach in the outer muscle layers may not only weaken the wall but may also disrupt normal oesophageal motility and produce functional obstruction[63]. By similar mechanisms, multiple pulsion diverticula have developed in patients with oesophageal muscular atrophy and dysplasia from progressive systemic sclerosis[16,17,27] and Ehlers–Danlos syndrome[65].

Clinical presentation

Symptoms associated with oesophageal pulsion diverticula vary considerably in type, frequency and severity. It is now well accepted that they correlate with an underlying motility disturbance[28,35] and are not primarily influenced by diverticular size[30]. Furthermore, symptoms are equally likely to be present with mid-oesophageal and epiphrenic pulsion diverticula[39,44,46]. They usually progress with time[4].

Dysmotility symptoms

Most symptoms are intermittent and may progress for many years before presentation[28,66]. The most common are dysphagia and regurgitation (*Table 2*). Dysphagia results from functional obstruction due to incoordinate motility and is the most common complaint. Significant weight loss, sometimes requiring hyperalimentation, may result[1,2,4,24,52,67]. Regurgitation of undigested food often accompanies dysphagia, and aspiration with a mortality risk may ensue[28,52]. Respiratory complaints, including nocturnal coughing, asthma-like symptoms, pneumonia and laryngitis, indicate aspiration; they may be the only presenting symptoms[41,52]. Retrosternal chest pain is thought to be pathognomonic of oesophageal spasm, but may require correlation with manometry to establish the diagnosis[68]. Heartburn, if present, appears mainly related to

Table 2 Symptomatology

Reference	Year	No. of patients	Dysphagia	Regurgitation or vomiting	Chest pain	Heartburn	Weight loss	Respiratory symptoms	Other	Minimal or absent
Habein *et al.*[33]	1956	121	20	24	1	–	6	7	10	97
Bruggeman and Seaman[20]	1973	80	9	8	10	–	–	–	4	41
Kaye[44]	1974	12	9	–	7	5	–	–	–	4
Rivkin *et al.*[43]	1984	34	24	22	–	–	12	–	–	3
Evander *et al.*[27]	1986	10	10	5	–	–	–	5	–	0
Streitz *et al.*[50]	1992	16	11	12	3	–	–	–	1	0
Fekete and Vonns[41]	1992	30	30	12	6	6	–	3	–	0
Altorki *et al.*[52]	1993	20	9	11	–	1	6	9	–	0
Benacci *et al.*[26]	1993	112	30	27	–	8	4	10	–	71
Castrucci *et al.*[40]	1998	51	35	34	–	16	–	6	–	16
Jordan and Kinner[42]	1999	25	10	14	4	11	–	6	–	5
Total		511	197 (39)	169 (33)	31 (6)	47 (9)	28 (5)	46 (9)	15 (3)	237 (46)

Values in parentheses are percentage of total number of patients studied stasis oesophagitis but is occasionally due to acid reflux[40,42,66,69].

Diverticular symptoms

Epiphrenic diverticula are the primary source of presenting symptoms in less than 20 per cent of patients[9,27,28,34,70]. Symptoms often present acutely, usually indicating a complication. Total or near-total dysphagia may result from a large diverticulum distended with food, compressing the adjacent oesophagus[4,28,61,67,70–72]. Disproportionate weight loss is common[1,2,4,24,46,63,67,72–74] and so escalation of dysphagia with increasing weight loss should raise the suspicion of an impending complication

Retention of food within a diverticulum may cause regurgitation or vomiting of old and undigested food[8,24,31,66,67,75], halitosis[50], retrosternal gurgling or angina-like chest pain[1,12,60,76–78]. More serious and potentially fatal manifestations include aspiration[24,31,52] (occasionally during induction of anaesthesia[1,4,35,41,52,66,79]), acute dyspnoea and stridor from pulmonary displacement[76], cardiac tachydysrhythmias from atrial compression[4,12,76,80] and diverticular rupture[22,81], and, rarely, tension pneumothorax[82]. The cause of atypical symptoms may remain obscure until the time of surgery[1,22,76].

Diverticular inflammation and ulceration may cause chest pain[28,77]. Ulcer formation rarely progresses to profuse haemorrhage[3,34,83,84] or perforation[22,85], both of which are life-threatening presentations. A diverticular ulcer may fistulate into the pleural space or a bronchus and can result in an empyema[3,27,52]. Malignant transformation in a diverticulum is rare but well recognized, manifesting as dysphagia, weight loss or haematemesis[86,87]. Although symptoms correlate with the presence of a motility disorder rather than diverticular size[26,30], large retentive diverticula frequently give rise to symptoms[20,22,27,34,41,52,81]. What is not clear is the proportion of large diverticula (more than 5 cm) that become complicated in this fashion.

Asymptomatic patients

The proportion of patients with pulsion diverticula who are asymptomatic is disputed. Up to 80 per cent of patients were reported by the Mayo Clinic and others to have insufficient symptoms to warrant treatment[26,33,66]. In other series fewer than half of the patients were asymptomatic (*Table 2*). Diverticula in asymptomatic patients are largely incidental findings and so the true number of patients with diverticula will remain underestimated[26,66,74,88–90].

Asymptomatic patients have been followed to determine their eventual outcome (*Table 3*). Over a 12-year period diverticular enlargement was noted in 16 per cent, but this is of uncertain significance[20]. In several studies none of the patients developed or had progressive symptoms[26,28,40]. Conversely, Hudspeth *et al.*[53] found that six of nine asymptomatic patients eventually became symptomatic and recommended surgery only when symptoms developed. Altorki *et al.*[52], however, strongly advocate operative intervention in all patients, even if asymptomatic, based on a high rate of aspiration in nine of 20 patients, three of whom developed life-threatening complications. One other patient who refused surgery died from aspiration pneumonia. Of note were five patients who presented with only pulmonary symptoms. In a review by Debas *et al.*[28] of 29 symptomatic patients who received no treatment, four aspirated and two subsequently died from pulmonary complications.

There is insufficient detail in the literature to help predict the natural history of asymptomatic disease, but less than 10 per cent of patients may develop symptoms or complications related to a diverticulum. The rare possibility of malignant change should be considered; many authors advise regular surveillance and barium oesophagograms, with treatment only if symptoms develop[19,35,53,54,81,91,92]. It is critical to assess carefully for pulmonary symptoms. Evidence of aspiration, even in the absence of oesophageal symptoms, is an absolute indication for operative intervention.

Table 3 Outcome for patients with minimal or absent symptoms

Reference	Year	No. of patients	Follow-up (months)	No change	New or worse symptoms	Lost to follow-up
Habein *et al.*[33]	1956	25	> 60	21	4	0
Debas *et al.*[28]	1980	7	n.s.	7	0	0
Hudspeth *et al.*[53]	1993	9	3–144	3	6	0
Benacci *et al.*[26]	1993	71	48–180	35	0	36
Castrucci *et al.*[40]	1998	16	42–99	13	0	3
Jordan and Kinner[42]	1999	5	48–228	4	1	0
Total		133		83 (62)	11 (8)	39 (29)

Values in parentheses are percentage of total number of patients studied. n.s., Not specified

Pathology

Diverticular morphology

Pulsion diverticula consistently develop on the right posterolateral border of the epiphrenic oesophagus and have a deficient muscularis propria. Eighty per cent of diverticula are 1–5 cm in diameter and the mean diameter of the diverticular mouth is 25 (range 15–45) mm[33]. A relatively narrow mouth and a dependent diverticular fundus are believed to encourage food retention and diverticular enlargement[42,54]. Diverticula larger than 5 cm are sometimes known as 'giant' diverticula[22,24,37,89], the largest reported diverticulum being 18 cm[72]. Approximately 10 per cent of patients will have multiple pulsion diverticula[6,20,26–29,33,41–43,52].

Inflammatory changes

Chronic diverticular stasis with bacterial overgrowth causes localized inflammation and ulceration, and may predispose to haemorrhage[3,83] or perforation[22,82,85]. Transmural inflammation may cause peridiverticular adhesions to adjacent structures, making operative dissection difficult[1,4,11,31,66,77] and predisposing to fistula and abscess formation[6,52]. The presence of a chronic inflammatory infiltrate[20,59,77,85], squamous hyperplasia[4,20,42,59,93], submucosal hypertrophy, fibrosis and vessel wall thickening[20,42], leukoplakia[28] and hyperkeratosis[20] have been described histologically.

Risk of malignancy

Carcinoma complicating epiphrenic and mid-oesophageal diverticula occurs sporadically and the overall risk to patients may be similar to that of the general population[69]. Between 30 and 40 cases of oesophageal carcinoma associated with pulsion diverticula have appeared in the English language literature[10,86,87,94–98]. Hoover[99] reported two cases in 185 patients (1·1 per cent), Goodman and Parnes[32] found one in 129 patients (0·8 per cent), and the Mayo Clinic up to 1976[6,28,45] reported diverticular carcinoma in three (0·7 per cent) of some 450 patients. There is no conclusive relationship between malignant risk and diverticular size or chronicity but the suspicion is that both are contributing factors. Chronic stasis is more likely in larger diverticula that empty poorly. Stasis and inflammation is believed to induce epithelial atypia[20,87,95,100,101]. Because of the false wall, diverticular malignant invasion may be early with lymph node involvement being common[10,86,95,97]. This may account for the poor prognosis of diverticular carcinoma. Where carcinomas are found in close proximity but not within diverticula, it has been proposed that diverticular refluxate may have induced the malignant change[97,101].

Other oesophageal tumours

Overall, 2–6 per cent of leiomyomas are found concurrently with oesophageal diverticula, but rarely within a diverticulum[26,28,29,42,62,71]. There is no strong aetiological link between the two, but an obstructing leiomyoma or one that causes pseudoachalasia may result in a pulsion diverticulum. A single case of malignant fibrous histiocytoma has been reported[26].

Hiatus hernia and gastro-oesophageal reflux

Hiatus hernia coexists in 33–75 per cent of patients with oesophageal diverticula[7,19,42,66]. This was initially thought to have aetiological significance, as reflux oesophagitis was believed to cause focal wall weakness and oesophageal spasm[7,19,42]. There is, however, a paucity of pH data and the prevalence of associated GORD remains poorly investigated. Castrucci *et al.*[40] found that nine (18 per cent) of 51 patients had GORD on selective 24-h oesophageal pH studies, of whom three had a recordable motility disorder. In many cases oesophagitis, heartburn and regurgitation may be attributable to oesophageal stasis rather than GORD. Peptic strictures may be associated with pulsion diverticula, but this represents a minority of cases[26,28,52,66]. No other convincing pathophysiological evidence exists to support a relationship between hiatus hernia, GORD and pulsion diverticula[66,69].

Investigations

Most oesophageal diverticula are found incidentally. A plain chest radiograph, contrast oesophagogram, endoscopy and manometry are considered standard investigations for assessing the oesophageal obstructive symptoms that accompany pulsion diverticula.

Chest radiograph

An oesophageal diverticulum is often not visible[12,59,88], or may appear as a mediastinal density or an air-fluid level on a plain chest radiograph[24,37,65,67,89]. These features are commonly misdiagnosed as a hiatus hernia[33]. Pneumonic changes and signs of abscess formation may accompany aspiration or an oesophagopulmonary fistula, but the aetiology may go unrecognized[2,77]. The plain radiological features are relatively non-specific and the possibility of an oesophageal diverticulum should be entertained when an air–fluid structure is seen on a chest film.

Contrast oesophagogram

Oblique views of a contrast oesophagogram best define diverticular number, location, diameter, shape and mouth size[1,102]. The filling and reflux dynamics of a diverticulum[11,20,42,66], and whether it causes oesophageal obstruction, may be demonstrated[2,8,24,61,67,69,71]. A persistent mucosal irregularity may indicate debris, inflammation, ulceration, fistulation or malignant change, and requires further examination by endoscopy[8,10,71,73,86,97]. A diverticular fistula may not be outlined and may only become obvious at surgery. The manner in which contrast agent is cleared from the oesophagus may help define a motility disorder, but a functional or mechanical cause of a stricture may not be differentiated. A radiological diagnosis of achalasia or diffuse oesophageal spasm can sometimes be made, but entirely normal peristaltic activity does not exclude the presence of a motility disorder[3,37,63,66]. Contrast studies are therefore unreliable for evaluating motility patterns[28,39,52]. Occasionally, epiphrenic diverticula may be misdiagnosed as a hiatus hernia, even on an oesophagogram[49,75,76].

Endoscopy

Endoscopy is recommended irrespective of radiological appearances[86,87,95]; it is essential for identifying oesophageal tumours or strictures as causes of dysphagia, and in differentiating radiographic irregularities while permitting biopsies for histology. Heterotopic tissue within a diverticulum suggests a duplication cyst[13,14]. Ulcers and malignant lesions not evident on contrast radiology may be visible on endoscopy. An attempt should be made to enter the diverticulum and visualize the mucosa, as failure to do so has resulted in missed carcinomas[86,87]. The risk of perforation from this manoeuvre is low and is more likely when a diverticulum is unknowingly entered[85,103]. Care should be taken when biopsying the false wall of a diverticulum. Endoscopy is a poor method of assessing oesophageal motility.

Manometry

Manometry is the 'gold standard' technique for diagnosing LOS dysfunction and oesophageal motility disorders; the diagnostic yields remain higher than those for radiographic studies[28] (*Table 1*). The presence of a sizeable diverticulum or a non-relaxing LOS may thwart repeated attempts to pass the manometry catheter across the sphincter[26,28,49], and an accurate assessment may not be possible. Correct placement of the catheter may be achieved under endoscopic guidance[40]. When manometry and other investigations fail to demonstrate a motility disorder, one should remain suspicious. With the exception of achalasia, most motility disorders occur intermittently and may not be evident during oesophagoscopy, contrast radiology or standard manometry[19,76]. Twenty-four-hour ambulatory manometry increases the diagnostic yield and accuracy of motility disorder diagnosis, particularly for diffuse oesophageal spasm and non-specific oesophageal motility disorder, and should be considered when other conventional methods have failed to diagnose a motility problem[40,68,104].

Oesophageal pH

Whether a 24-h oesophageal pH study is required depends on whether acid reflux is thought to be contributing to symptoms. It is difficult to imagine how gastric reflux may occur across a supercompetent LOS in achalasia, but GORD, without stricture complication, can occur concurrently with pulsion diverticula[40,66,69,92]. Therefore, a positive pH study does not necessarily preclude the presence of a major motility disorder[40,69].

Other investigations

Other investigations should be used selectively[5,105]. They may be helpful in evaluating atypical symptoms or findings, whether a diverticulum is known to exist or not[11]. Bronchoscopy may exclude primary bronchial pathology associated with a diverticulobronchial fistula. Computed tomography may define a mass lesion arising from a perforated or malignant diverticulum[86]. Endoscopic ultrasonography has been used to study diverticular wall structure and identify regions of muscular hypertrophy[9,37], but its role in the management of the lesion has not been established. It may be helpful when staging a diverticular carcinoma. Radionuclide transit studies are of curiosity value only[63,106].

Despite investigations, the presence of a pulsion diverticulum and related motility disorder may occasionally remain undiagnosed until surgical exploration. Examples have often involved acutely ill patients following diverticular rupture or cardiorespiratory embarrassment and the cause may be confused with a complicated paraoesophageal hiatus hernia[76,86,103]. It is prudent therefore to consider an oesophageal cause for any atypical or unexplained acute intrathoracic pathology.

Operative principles

There is consensus that surgical treatment should be reserved for symptomatic patients. What the standard operative management should be remains a source of diverse opinion. The published data were reviewed to determine which operative approach offered the best outcome.

Preoperative considerations

A thorough assessment of symptoms, oesophageal motility and the diverticulum is required. Nutritional supplements for significant weight loss may be warranted. The possibility of diverticular complications including malignancy should be considered, and large retentive diverticula must be emptied to prevent aspiration during anaesthesia. Surgical access should allow for any number of intended procedures to be performed, including diverticulectomy, myotomy and fundoplication. These techniques are well described elsewhere in the literature.

Selective or routine diverticulectomy

Few surgeons would consider diverticulectomy unnecessary[69]. Many others only excise a diverticulum if there is diverticular inflammation, ulceration, dysplasia, fistulation, or if the lesion is suspected or known to cause symptoms[27,29,41,47,51,107]. Invasive carcinoma warrants oesophagectomy. Retentive or large diverticula are also resected, even if asymptomatic, as the risk of aspiration and complications from food retention are considered to be significant[26,30,41,52]. This selective approach is argued to reduce the incidence of suture line leaks and strictures from unnecessary diverticulectomies. Others suggest that diverticular imbrication or pexis would similarly reduce these risks, although the risk of malignant change may remain[27,30,42,52,53]. It is unclear how many authors advocate routine diverticulectomy as the aforementioned indications commonly exist, and the reasons for diverticulectomy are frequently unspecified[4,26,28,41,43]. Routine diverticulectomy as an adjunct to myotomy, however, appears to add negligible morbidity (*Tables 4* and *5*), and addresses the concerns of long-term diverticular complications including the risk of malignancy.

Diverticulectomy with or without myotomy

A comparison of published results illustrates higher rates of postoperative leak from a diverticulectomy suture line, and a higher incidence of persistent or recurrent symptoms and diverticular recurrence following diverticulectomy without a myotomy (*Tables 4* and *5*). Nearly 7 per cent of all patients in these studies had presented with recurrent diverticula following previous excision without myotomy[26,43,52,53,66]. Suture line leaks were associated with an inordinate mortality rate of 27 per cent, irrespective of whether

Table 4 Results following simple diverticulectomy

Reference	Year	No. of patients	Leaks	Deaths*	Recurrent symptoms	Recurrent diverticula
Jordan and Kinner[42]	1999	6	1	0	1	0
Castrucci *et al.*[40]	1998	5	1	1	0	0
Peracchia *et al.*[54]	1994	5	2	0	0	0
Benacci *et al.*[26]	1993	7	0	0	1	0
Streitz *et al.*[50]	1992	3	1	0	0	0
Fekete and Vonns[41]	1992	10	1	1	0	0
Hudspeth *et al.*[53]	1993	1	0	0	0	1
D'Ugo *et al.*[51]	1992	5	1	1	1	0
Evander *et al.*[27]	1986	1	0	0	0	0
Rivkin *et al.*[43]	1984	6	0	0	1	2
Fegiz *et al.*[29]	1984	1	0	0	0	0
Debas *et al.*[28]	1980	1	1	0	1	0
Luosto *et al.*[85]	1978	20	1	1	2	4
Kadlubowska[81]	1976	7	0	0	0	0
Bruggeman and Seaman[20]	1973	4	1	1	3	0
Garcia *et al.*[49]	1972	7	1	0	4	2
Allen and Clagett[35]†	1965	27	5	1	11	4
Naclerio[45]	1957	3	0	0	0	0
Harrington[1]‡	1949	2	1	0	1	1
Total		121	17 (14)	6 (5)	26 (21)	14 (12)

Values in parentheses are percentage of total number of patients studied. *Leak-related deaths; †includes data from Habein *et al.*[34] and Harrington[1]; ‡excludes data included in Allen and Clagett[35] myotomy was performed or not, and was 35 per cent following simple diverticulectomy compared with 15 per cent in those who had a myotomy. The Mayo Clinic[35] first highlighted the poor results following simple diverticulectomy. Several authors still advocate diverticulectomy without myotomy in patients who have no demonstrable motility disorder, citing good results and reduced risk of leaks from unnecessary myotomies[4,29,40,53]. Suture line leaks and recurrent symptoms, however, have occurred in patients following selective diverticulectomy based on absent motility disorders[26,40,92]. For leaks following diverticulectomy with myotomy there is a suspicion that an insufficient myotomy, particularly in the subdiverticular region, may have failed to relieve distal obstruction[29,35,41]. Benacci *et al.*[26] even questioned whether a loose Nissen fundoplication after excision and myotomy may have created a distal obstruction sufficient to cause a suture line leak. Current evidence does not favour simple diverticulectomy without myotomy and emphasizes the need for accurate preoperative motility assessment and attention to the placement of the myotomy.

Selective or routine myotomy

Myotomy has become the mainstay of surgical treatment for oesophageal motility disorders. Although many surgeons would not perform a diverticulectomy without a myotomy, many of the same surgeons argue that a myotomy should only be performed if there is a demonstrable motility disorder[4,56,64,76] (*Tables 4* and *5*). They deny there is any advantage of a myotomy in the absence of a motility disorder, but rather a risk of disrupting normal peristalsis. By avoiding unnecessary myotomies, a selective approach may reduce postmyotomy leaks and gastro-oesophageal reflux. Conversely, other surgeons are equally committed to performing a myotomy routinely, irrespective of whether or not a motility disorder can be demonstrated[5,18,26,30,41,43,90,101] (*Table 5*). They argue that pulsion diverticula invariably arise from a functional obstruction and that preoperative investigations may not always identify motility disorders. The results following selective and routine myotomy are comparable and fail to demonstrate that one approach is inferior to another.

Tailored myotomy

Many types of myotomy have been recommended to treat pulsion diverticula, but there is a strong suspicion that insufficient cardiomyotomies have been responsible for diverticulectomy site leaks[29,41]. This has influenced some, irrespective of the manometric abnormality, routinely to extend the myotomy across the LOS for 2 cm or more on to

Table 5 Results following diverticulectomy with myotomy

Reference	Year	No. of patients	Leaks	Deaths*	Recurrent symptoms	Recurrent diverticula
Jordan and Kinner[42]†	1999	9	0	0	0	1
Castrucci *et al.*[40]†	1998	12	1	0	1	0
Altorki *et al.*[52]‡	1993	14	0	0	1	0
Benacci *et al.*[26]	1993	22	6	2	3	0
Streitz *et al.*[50]†	1992	13	0	0	0	0
Fekete and Vonns[41]	1992	11	1	0	2	0
Hudspeth *et al.*[53]†	1993	8	1	0	0	0
D'Ugo *et al.*[51]‡	1992	6	0	0	0	0
Fatsis *et al.*[107]	1991	5	0	0	0	0
Mulder *et al.*[66]‡	1989	4	0	0	0	0
Evander *et al.*[27]‡	1986	8	0	0	2	0
Rivkin *et al.*[43]	1984	3	0	0	0	0
Fegiz *et al.*[29]†	1984	10	3	0	4	0
Debas *et al.*[28]	1980	17	0	0	0	0
Kadlubowska[81]	1976	3	0	0	0	0
Nicks[108]	1976	10	0	0	0	0
Bruggeman and Seaman[20]	1973	7	0	0	0	0
Garcia *et al.*[49]	1972	4	0	0	0	0
Allen and Clagett[35]‡§	1965	13	1	0	0	0
Total		179	13 (7)	2 (1)	13 (7)	1 (1)

Values in parentheses are percentage of total number of patients studied. *Leak-related deaths; †selective myotomies; ‡routine myotomies; §includes data from Habein *et al.*[34] and Harrington[1] the cardia to ensure that there is no residual oesophageal obstruction[27,30,41,52]. An antireflux procedure is usually added. Others have attempted to preserve the antireflux mechanism if the LOS is known to be manometrically normal[40,50], or to limit the myotomy to less than 10 mm on to the cardia if functional obstruction involves the LOS[26,53]. Several surgeons have warned against a myotomy when GORD or an incompetent LOS is demonstrated, but it is unclear whether they advocate antireflux surgery as primary operative treatment for these patients[40,42]. Surgeons have also tailored the myotomy according to manometric characteristics. A cardiomyotomy is performed for achalasia or hypertensive LOS disorders, but the proximal and distal limits vary between individual operators[26,40,50,53,66]. An oesophagomyotomy is preferred for diffuse oesophageal spasm or non-specific oesophageal motility disorder but may commence from any level at or below the aortic arch. Some surgeons prefer to confine the myotomy to the manometric region of dysmotility, while others dispute whether it is valid to rely on manometry in this way[19]. Other operators largely ignore the manometric details and site the myotomy according to the level of the diverticulum[11,19,29,109]. The myotomy starts either just above the level of the proximal lip of the diverticular mouth, or at the inferior lip, and ends distally on to the cardia. This approach depends on the notion that a pulsion diverticulum forms just proximal to an obstruction and that a subdiverticular myotomy best treats the pathology. There are a few who undertake a long 'indiscriminate' oesophagocardiomyotomy irrespective of the manometric findings and the diverticular location, and obtain a satisfactory outcome[31,41,52,56]. Overall, the results from the various myotomies are difficult to compare. An operative principle worth considering is that the distal or subdiverticular portion of a myotomy may significantly influence outcome and deserves close attention when being performed.

Antireflux procedures

The debate continues about whether or not a myotomy should include a fundoplication. The risk of GORD after myotomy, particularly when it extends well on to the cardia, is appreciated but perhaps poorly quantified with pH studies. The incidence of acid reflux symptoms appears significantly less when fundoplication is added under these circumstances (*Table 6*). Routine fundoplication may also prevent stricture formation from acid reflux that has occasionally required oesophageal resection[49]. Many agree that patients who have proven GORD should be considered for a fundoplication[26,29,40,43,92]. Although there is consensus that a partial or patch fundoplication is preferable to a complete wrap to reduce the risk of obstructive complications[30,76,92], there is no evidence to justify fears of postfundoplication leaks (*Table 6*).

Table 6 Results following myotomy with and without fundoplication

		Myotomy without fundoplication			Myotomy with fundoplication		
Reference	Year	No. of patients	Heartburn	Leak	No. of patients	Heartburn	Leak
Rosati *et al.*[92]	1998	–	–	–	4	0	0
Castrucci *et al.*[40]	1998	–	–	–	9	0	1
Benacci *et al.*[26]	1993	18	5	3	6	2	3
Altorki *et al.*[52]	1993	–	–	–	17	2	0
Hudspeth *et al.*[53]	1993	8	0	1	–	–	–
Streitz *et al.*[50]	1992	10	2	0	–	–	–
D'Ugo *et al.*[51]	1992	–	–	–	12	0	0
Fekete and Vonns[41]	1992	1	0	0	14	4	1
Mulder *et al.*[66]	1989	3	1	0	1	0	0
Evander *et al.*[27]	1986	–	–	–	8	0	0
Fegiz *et al.*[29]	1984	–	–	–	3	1	1
Rivkin *et al.*[43]	1984	1	0	0	3	0	0
Debas *et al.*[28]	1980	5	0	0	12	0	0
Garcia *et al.*[49]	1972	1	0	0	3	0	0
Allen and Clagett[35]	1965	4	0	0	6	0	1
Total		51	8 (16)	4 (8)	98	9 (9)	7 (7)

Values in parentheses are percentage of total number of patients studied

Minimal access techniques

Minimal access surgery has been successful in the treatment of a range of benign oesophageal diseases[110]. Early results from laparoscopic and thoracoscopic techniques for oesophageal pulsion diverticula are similar to those of open surgery (*Table* 7). Postoperative leaks have occurred in 8 per cent of patients[79,110] and symptom relief has been achieved in all patients reported so far. The potential for pneumothorax appears to be associated particularly with laparoscopic transhiatal dissection and has been noted in two of 13 procedures[11,112]. Ease of access, improved visualization, reduced wound-related morbidity and improved recovery rates are the perceived advantages of minimal access procedures[79,92,103,111,113]. Laparoscopic techniques avoid single-lung ventilation but giant diverticula or those above the epiphrenic region are best approached thoracosopically[79,92,110,111]. Dissection of large or adherent diverticula may be more challenging but this has not hindered the early success with minimally invasive procedures[11]. These techniques may yet prove to be the new standard for the future but further evaluation is necessary.

Conclusion

There is convincing evidence to suggest that oesophageal diverticula and their associated symptoms are sequelae of an underlying motility disorder. The precise pathophysiological processes are not fully understood. Why do pulsion diverticula occur in some patients and not others? Why are associated symptoms so variable, if present at all? It is important to establish the characteristics of any underlying motility disorder and manometry achieves this best. Even when not demonstrable, the suspicion of dysmotility should remain. It is important to exclude the remote possibility of diverticular malignancy as this significantly influences surgical management.

The decision to intervene only when symptoms are present is well supported in the literature. The most significant morbidity and mortality risks associated with non-intervention result from aspiration. Therefore evidence of aspiration mandates surgical intervention, even in the absence of oesophageal symptoms. Conservative management of asymptomatic patients should include regular clinical and radiological review, although the proportion of patients who will eventually develop symptoms is probably low.

The disease spectrum does not allow for a standard operative approach in all cases. The most common causes of operative death are perioperative aspiration and postoperative leaks. It is clear that the historical preference for simple diverticulectomy is inadequate. The documented rates of early postoperative leak and mortality are significantly higher, as is the incidence of unrelieved symptoms and diverticular recurrence. The data strongly support myotomy as the mainstay of treatment, irrespective of how the diverticulum is managed. The majority of reports favour routine diverticulectomy, although there is no evidence that selective diverticulectomy results in a suboptimal outcome. The placement of a myotomy is dictated by the manometric findings, the function of the LOS, the location of the diverticulum and operator preference. The proximal extent of a myotomy appears to impact little on outcome. What seems crucial is the subdiverticular portion, which ensures that distal obstruction is relieved. Poor results have been attributed to inadequate myotomy in this region. Whether an antireflux procedure needs to be added remains widely debated. Fundoplication reduces the risk of acid reflux for myotomies that extend on to the cardia for more than 2 cm.

Table 7 Minimal access surgery for oesophageal pulsion diverticula

Reference	Year	No.	Procedure	Conversion to open	Complications	Symptom relief
Chami *et al.*[111]	1999	1	L–M,F	–	–	1
Eubanks and Pellegrini[112]	1999	3	L–D,M,F × 3	–	1 pneumothorax	3
Tinoco *et al.*[103]	1999	1	L–D	–	–	1
Myers and Dempsey[11]	1998	3	L–D,M,F × 2	1*	1 pneumothorax	3
Saw *et al.*[113]	1998	1	T–D,M,F	–	–	1
Rosati *et al.*[92]	1998	4	L–D,M,F × 4	–	–	4
Gul *et al.*[79]	1997	1	T–D	–	1 radiological leak	1
Stuart *et al.*[15]	1996	1	T–D	–	–	1
Peracchia *et al.*[110]	1995	2	L–D,M,F × 2	–	–	2
Peracchia *et al.*[54]	1994	8	T–D × 6	2†	1 clinical leak	8
Total		25	22	3	4	25

*Abdominal adhesions from previous surgery; †unable to collapse lung. L, laparoscopic transhiatal; T, thoracoscopic; M, myotomy; F, fundoplication; D, diverticulectomy

There is some consensus that a partial wrap or patch is preferable to minimize the risk of postfundoplication dysphagia. The fear of postfundoplication suture line leaks appears unfounded. It is appropriate to consider an antireflux procedure when abnormal acid reflux is demonstrated before operation.

The early experience with minimal access techniques in treating pulsion diverticula suggests potential benefits without compromising effectiveness or safety. The indications and principles for such surgical intervention remain the same as those for an open approach. Specific difficulties encountered with the laparoscopic and thoracoscopic procedures appear to be few and minor, and minimal access techniques have the potential to become the standard operative approach for this condition.

It is evident that many issues regarding the pathogenesis and management of oesophageal pulsion diverticula remain unresolved. Because of the uncommon nature of the lesions comparative studies are not possible and critical appraisal of new evidence remains the only means of determining current best practice.

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Review

Quality of life as an outcome measure in surgical oncology

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Background: There is a growing interest in assessing the impact of a disease and the effect of a treatment on a patient's life, expressed as health-related quality of life (HRQoL). HRQoL assessment can provide essential outcome information for cancer surgery.
Methods: The core of this review is derived from a literature search of the Medline database.
Results: Three types of HRQoL instrument can be distinguished: generic, disease specific and symptom specific. There are criteria against which HRQoL instruments may be evaluated. The instrument chosen must be reliable, valid and sensitive to change.
Conclusion: HRQoL measurement may be useful in identifying the optimal surgical procedure. It may also be of help in deciding whether surgery in patients with limited life expectancy should still be considered. No HRQoL instrument fits all the recommended conditions or is suitable in all clinical situations. Using the appropriate instrument is essential to arrive at valid and clinically meaningful outcome measures.

Paper accepted 8 January 2001

British Journal of Surgery 2001, 88, 643–652

Introduction

For many years the outcomes of medical treatments have been measured primarily in terms of death, disability or cure but it is increasingly acknowledged that health-related quality of life (HRQoL) is an important additional outcome measure. Over the past 30 years several HRQoL instruments have been developed and most of them applied to studies of cancer or chronic diseases, generally to compare treatment outcomes in the context of clinical trials. A wide variety of instruments is currently available, which leaves the researcher with a confusing array of options.

So far, the application of HRQoL instruments in evaluating treatment outcomes in surgical oncology is not routinely applied. The main objective of this review is to present to researchers and practitioners in the field of surgical oncology a brief overview of the different aspects of HRQoL, how HRQoL is measured, and the different instruments developed to measure it.

Quality of life measurement

Apart from health-related factors, quality of life also includes non-health-related elements, such as personal income, location of residence and leisure time. However, in medicine there is a need to measure HRQoL, comprising all the areas that can be affected by aspects of health.

There is a consensus that HRQoL is a multidimensional construct. Generally, there are three principal aspects of HRQoL: physical, psychological and social[1]. These aspects are called *domains*. The physical domain refers to perceived and observed bodily function or its disruption. Examples are pain, nausea and mobility. Psychological functioning includes both positive and negative effects, for example a patient's concerns, distress and mood. The social domain refers to the ability to perform activities related to a societal role. These are activities of daily life with respect to responsibilities in and outside of the home, including those associated with family, friends and colleagues. Besides the measurement of HRQoL by means of registration of the actual conditions measured on these three main domains, a global HRQoL assessment is recommended. Such a global HRQoL refers to the subjective appraisal of one's own health as a whole.

Types of quality of life instrument

This article will focus on evaluative HRQoL instruments used in clinical trials. Three types of instrument can be distinguished: generic, disease specific and symptom specific. Generic instruments are designed to be used for all kinds of diseases and medical treatments. These allow comparisons to be made across conditions and interventions. However, generic instruments may fail to capture those aspects of patients' experience that are of clinical interest in a specific clinical setting. They cannot be used to evaluate HRQoL changes in detail because they are not sensitive enough and may lack particular relevant subdomains. Examples of generic instruments are the Short Form 36-item Health Survey, Sickness Impact Profile and the Nottingham Health Profile[2]. Disease-specific instruments are designed to assess HRQoL in specific diagnostic groups or patient populations. The domains and items chosen for these instruments are directly related to the impairments caused by the disease process or its intervention. Therefore, disease-specific instruments are likely to be more responsive to change. Examples are the Functional Living Index, Rotterdam Symptom Checklist, QL Index and Cancer Rehabilitation Evaluation System[3]. Symptom-specific instruments focus solely on the symptoms produced by a given disease process without addressing other HRQoL issues. It can be argued that they do not formally satisfy the HRQoL definition. Examples of a symptom severity instrument are the Gastrointestinal Symptom Rating Scale[4] and the McGill Pain Questionnaire[5].

Choosing an HRQoL instrument is based *inter alia* on the goals of the proposed research. If the aim is to determine whether a particular therapy improves symptoms, a short symptom-specific instrument will be sufficient. If broader effects of a specific disease process are to be studied, a disease-specific instrument may be more appropriate. To be able to compare the results of one study with another, a generic instrument may be more appropriate. Most often, a combination of a generic and disease-specific instrument is used (*Table 1*).

Evaluative HRQoL instruments encompass multiple domains and are therefore commonly indicated as profile measures. Opposed to this, health economists have developed so-called preference-based HRQoL instruments. A distinguishing feature of a preference-based HRQoL instrument is its potential to assign a single numerical value (or utility) to any health status of a particular patient. Based on a descriptive classification (i.e. domains or attributes) a preference index (utility) can be estimated that expresses the overall preference of the classified health state. This utility on a scale from 0 to 1·0 (0, death; 1·0, perfect health) is obtained by applying a predetermined multiattribute utility function. Utility figures are required to calculate quality-adjusted life years (QALYs) for cost–utility analysis; QALYs integrate mortality and morbidity to express health status in terms of equivalents of well years of life[6]. QALYs are appealing, because they provide a relatively simple means of reflecting the HRQoL effects of medical interventions and enable comparisons of interventions that have very different types of outcome. For economic evaluations, the cost of different treatment regimens can be related to the benefits of the regimens by performing a cost-effectiveness analysis[7]. QALYs are combined with the costs of each strategy to arrive at the cost per QALY gained.

European Organization for Research and Treatment of Cancer approach

The European Organization for Research and Treatment of Cancer (EORTC) has proposed a modular approach[8]. This consists of a core questionnaire supplemented by a module. The core questionnaire is a patient self-reported HRQoL questionnaire covering physical, emotional and social health aspects, and symptoms relevant to a broad range of patients with cancer. This core questionnaire is supplemented by disease- and/or treatment-specific instrument(s) to assess issues not (sufficiently) covered by the core instrument. An example is the EORTC QLQ-PAN26, designed for patients with pancreatic cancer. Adoption of this modular assessment strategy is intended to reconcile two principal requirements of a HRQoL measure: (1) a

Table 1 Types of quality of life instrument

Type of instrument	Application	Examples
Generic instrument	Comparisons across health conditions and interventions	Short Form 36-item Health Survey, Sickness Impact Profile, Nottingham Health Profile
Disease-specific instrument	Specific diagnostic groups and patient populations	Functional Living Index, Rotterdam Symptom Checklist, Cancer Rehabilitation Evaluation System, EORTC QLQ-C30, FACT-G
Symptom-specific instrument	Symptoms of a certain disease process, e.g. pain	Gastrointestinal Symptom Rating Scale, McGill Pain Questionnaire

EORTC, European Organization for Research and Treatment of Cancer; FACT-G, Functional Assessment of Cancer Therapy – General sufficient degree of generality to allow for cross-study comparisons, and (2) a level of specificity adequate for addressing those research questions of particular relevance in a given clinical trial[9].

The most up-to-date version of the core HRQoL questionnaire currently available is the EORTC QLQ-C30, version 3.0. It consists of 30 items comprising five functional scales (physical, role, cognitive, emotional and social), three symptom scales (fatigue, pain and nausea/vomiting), a global health and HRQoL scale, and a number of single items assessing symptoms (dyspnoea, loss of appetite, sleep disturbances, constipation and diarrhoea) and perceived financial impact of the disease. In this version for all items four or seven response alternatives are offered.

Functional Assessment of Cancer Therapy – General

The Functional Assessment of Cancer Therapy – General (FACT-G) may be viewed as the US counterpart of the EORTC instrument. It is a well validated and reliable HRQoL instrument specific to patients with cancer[10]. It has been used extensively in North America and, with many foreign language translations available, has also found its place in European and worldwide studies. This instrument adheres to a similar concept, namely a modular approach with a generic core questionnaire in combination with disease-specific modules, for example for use with breast cancer (FACT-B).

The generic instrument (FACT-G, version 2) consists of 28 items covering physical, emotional and social health aspects and symptoms relevant to a broad range of patients. Five or ten response alternatives are offered per item. The EORTC QLQ-C30 and FACT-G are different with respect to the phrasing of the items; the EORTC instrument uses questions while the FACT-G uses statements. Kemmler *et al.*[11] have compared the two instruments on the basis of empirical data. The EORTC QLQ-C30 and FACT-G were found to measure markedly different aspects of HRQoL, despite considerable overlap. This suggests that neither of the instruments can be replaced by the other and that a direct comparison of results obtained with the two instruments is not possible.

Measurement properties of quality of life instruments

HRQoL instruments should meet three essential methodological properties: reliability, validity and responsiveness[12,13]. The first property, reliability, refers to the extent to which an instrument is free of measurement error (random error). Basically, there are two methodological approaches to estimate the reliability of an instrument: test–retest and internal consistency techniques[14]. Test–retest of an instrument is carried out by repeated examinations measuring an unchanged characteristic. Internal consistency refers to the degree of association among items addressing equivalent concepts. Most researchers prefer an instrument to have a reliability coefficient above 0·80.

Validity of an HRQoL instrument is an important aspect, perhaps the most crucial. Validity is defined by the extent to which an instrument measures what it is supposed to measure[15]. The concept refers to the systematic measurement error. There are three main types of validity: content, criterion and construct. Content validity is non-analytical and deals with the basic question 'Is the instrument really measuring what it is intended to measure?' Criterion or predictive validity is determined analytically and only applicable if there exists another method that can be identified as superior, i.e. a 'gold standard'. If there is no gold standard available, the HRQoL instrument should be evaluated by construct validity. Construct validity refers to the incorporation of those components or dimensions in the test that are hypothesized to underlie the concept that is being assessed.

The third methodological property that a HRQoL instrument should meet, and that has only relatively recently received attention, is responsiveness. Responsiveness, or sensitivity to change, refers to the extent to which an instrument is able to detect and measure changes in HRQoL over time or after an intervention. To be of value, an instrument should be stable when no change occurs, but reveal changes in cases of improvement or deterioration in a person's HRQoL. Two structural characteristics will aid detection of changes in HRQoL. First, the more items a scale has, the more responsive to change it will be. Second, offering respondents a range of response alternatives for each item will make the scale more responsive to changes in HRQoL. Five items per domain is generally accepted as satisfactory for detecting changes; five response categories per item are recommended. Although this approach is well defined conceptually, there are still some shortcomings from an analytical point of view.

Besides methodological properties there are some practical issues that should be considered. A HRQoL instrument needs to be practical. This characteristic refers to the ease with which the instrument can be used. The questionnaire should not be too long if unanswered items are not to be encountered. In addition, an instrument must be appropriate for the health problem and the likely range of effects of the treatment being investigated. The research question has to be related to the type of HRQoL instrument.

A substantial number of instruments published and in use have not been evaluated for all the characteristics mentioned above. Ad hoc instruments should therefore be viewed with caution. Researchers must know in advance how the data will be scored and analysed before they incorporate HRQoL assessment into studies (*Table 2*).

Methodological issues in measuring quality of life

As noted above, there is no clear-cut definition relating to the concept of HRQoL and so there is no 'best' HRQoL measure. Nevertheless, there is consensus about the general criteria that an instrument must fulfil. HRQoL instruments consist of a variable number of domains, usually about three (physical, psychological and social). Each domain gathers information focused on a particular HRQoL aspect. Each domain is subdivided into a number of questions, referred to as *items*.

Responses to the items may be collected by a categorical scale or a visual analogue scale[16]. Categorical scales provide a number of prompts, each with a numerical score. The simplest form is 0 for no and 1 for yes. More often there are three, four or five categories of response per item. The visual analogue scale is a line of standard length with extremes of response indicated at each end. The subject is asked to mark the line at an appropriate point and the score is obtained by measurement of the distance from one end. Visual analogue scales require a little more explanation to subjects and are somewhat more difficult to analyse, but they provide a good range of responses. Categorical scales are relatively easy to score but may be rather unresponsive to differences if the range of responses is too limited[1].

The time frame of the instrument is the period that the respondent is asked to consider in forming a response. There should be a balance in selection of the time frame such that it is possible to detect differences and minimize short-term fluctuations that do not represent real change but simply create noise in the data. A time frame such as the past week has often been used.

As most HRQoL instruments comprise multiple domains and/or multiple HRQoL instruments are often used together, statistical testing should not be conducted in a conventional manner. Instead of testing each domain and/or instrument separately, adjustments for multiple testing should be made by reducing the significance level of statistical testing to overcome the possibility of detecting an apparently statistically significant effect by chance. Various corrections are available (e.g. Bonferroni).

Timing of assessment of HRQoL must be scheduled carefully and is clearly related to the study design and the disease. In general, a minimum of three assessments is required to capture relevant changes in HRQoL over time in a clinical trial. The first assessment is one that should take place before the start of treatment and randomization (baseline), if applicable. The first assessment, although not a baseline in the true sense of the word, serves as such (a true baseline would be an assessment before the diagnosis of cancer). Furthermore, pretreatment HRQoL may be predictive of HRQoL during treatment and of survival[17,18]. The second assessment is during treatment, when treatment-related side-effects are expected to be at their height. The third assessment is at the end of the treatment. For most studies it is worthwhile evaluating the long-term effects of a treatment. Therefore, a follow-up at 6–12 months is often recommended. In addition, timing of assessment is closely related to the statistical analyses being carried out. Because the course of a particular type of cancer may be very different to that of other types of cancer, or because the course of the disease for individual patients may

Table 2 Measurement properties of quality of life instruments

	Description/comment
Methodological properties*	
Reliability	Extent to which an instrument is free of measurement error (random error) *Test–retest, internal consistency*
Validity	Extent to which an instrument measures what it is supposed to measure (systemic measurement error) *Content, criterion and construct validity*
Responsiveness	Extent to which an instrument is able to detect and measure changes over time or after an intervention *Stable when no change occurs, reveals changes in cases of improvement or deterioration*
Practical issues†	
Length	Limited, because otherwise unanswered items are encountered *Containing no more than 30 items*
Appropriateness	The type of instrument being used should be related to the research question

*Refers to the scientific value of the instrument; †refers to the ease with which the instrument can be used be unpredictable, the measurement of HRQoL may require a special study design (for example, repeated measurement at a fixed interval or measurement if an event occurs) in combination with specific analytical techniques.

Missing data during follow-up is a frequent problem encountered in longitudinal studies. Although special software programs exist to overcome this, at least partially, the best strategy is to try to prevent the occurrence of missing data as much as possible. Methodologies for handling missing data are still under development[19].

Compliance with completing HRQoL instruments may form an obstacle to their successful implementation. If possible, the instruments should have the following characteristics: (1) be easy to understand, (2) take less than 10 min to complete, (3) contain not more than 30 items, and (4) be self administered[20]. Moreover, attention should be given to the feasibility and completeness of data collection.

To achieve semantic equivalence, standardized translation procedures are required. An international guideline that seems to have become the standard for the translation of HRQoL instruments is based on the following procedure. The process consists of two forward translations of the source version, two back translations, lay assessment, and the production of a full report describing each stage of the process. Cultural adaptations of existing official versions follow a procedure of review of the 'mother' language version by a translation consultant, lay assessment, and the production of a full report describing the process. Any new translation should, if possible, be undertaken in close cooperation with the developers of an instrument.

Quality of life and surgical oncology

Measuring the results of surgery

Surgical outcome has traditionally been evaluated by measuring two basic variables, mortality and morbidity. Goligher[21] acknowledged that surgeons often adopt too simplistic an approach to the outcome of their efforts and are frequently content to judge results in terms of operative mortality rate, immediate operative morbidity rate and, in the case of operations for malignant disease, length of survival. Clinicians trained to obtain and rely on objective data sometimes have difficulty accepting the measurement of subjective evaluations. HRQoL should be considered as one of several possible clinical outcomes of interest. Its measurement can serve as an addition to measures of survival, complications and side-effects.

In surgical oncology, HRQoL measurement may be of help in identifying the optimal surgical procedure. Studies of HRQoL after different operations for colorectal cancer, breast cancer, gastric cancer and limb sarcoma may be regarded as examples. On the other hand, HRQoL assessment may also be useful in deciding whether surgery should still be considered for patients with limited life expectancy. For example, HRQoL assessment after operations for advanced pancreatic and oesophageal cancer may provide a significant outcome measure. Some examples of surgical oncology HRQoL are presented below.

Quality of life after treatment of colorectal cancer

A literature review of the HRQoL of patients with colorectal cancer undergoing surgery indicated that none of the studies so far performed employed standardized HRQoL instruments tailored to the needs of the patients[22].

Ulander *et al.*[23] have performed an exploratory study examining HRQoL in patients undergoing surgery for colorectal cancer. Two validated instruments were used, the EORTC QLQ-C30 Core Questionnaire and the Katz'/Hulter Åsberg Index of Independence in ADL (activities of daily life). These instruments were being used before operation and at follow-up after 5–8 months. Overall small differences were found between preoperative and follow-up results in the domains of HRQoL and Independence in ADL. Few of the findings of differences in HRQoL domains and Independence in ADL were statistically significant. The authors concluded that a modular approach for HRQoL of patients with colorectal cancer is needed.

To perform more methodologically sound studies, the EORTC developed a disease-specific HRQoL module for use in colorectal cancer[8]. The module includes primarily disease symptoms and side-effects related to different treatment modalities (i.e sphincter-saving resection, rectum extirpation, radiotherapy and chemotherapy). Additionally, HRQoL aspects that can be affected by (surgical) treatments (i.e. body image and sexuality) or that are related to stage of disease (i.e. future perspective) are also included. The module (QLQ-CR38) consists of 38 items. This module was tested and the results lend support to its clinical validity as a supplementary questionnaire for assessing specific HRQoL issues relevant to patients with colorectal cancer.

Despite heterogeneity in surgical techniques and study procedures, methodological shortcomings, and the need for additional confirmation of these results, some relatively consistent findings about the long-term effects of surgical procedures emerge from several studies[22]. For example, with regard to the issue of sphincter saving it is observed that a sizeable percentage of both patients with a stoma and patients with intact sphincters report limitations in all areas of HRQoL. Although both groups often report their general health state to be reasonably good, they are both troubled by frequent or irregular bowel movements and diarrhoea. Patients with a stoma report higher levels of generalized forms of distress and a more negative body image. These problems tend to be commoner in younger patients and in women. Colorectal cancer and its treatment can have an adverse effect on social functioning; patients with a stoma more often report restrictions in this respect.

Quality of life after treatment of breast cancer

Breast-conserving therapy (BCT) is now a well established alternative to a modified radical mastectomy (MRM) for the treatment of early-stage breast cancer. Since the first publication of clinical trials describing no difference between BCT and MRM with respect to duration of survival[24,25], discussion of the physical, psychological, social, occupational and sexual impact of the different treatment options has continued. Initially, the general belief was that BCT would provide greater benefit because of the physical and emotional importance a woman attaches to her breasts[26]. Kiebert *et al.*[27] described in their review that ten of the 12 studies that investigated the effect of treatment on body image reported positive outcomes with respect to body image in the BCT group. The remaining two studies found no difference between the two treatment groups with respect to body image. In the same review, six of eight studies that investigated fear of recurrence and death showed no difference between the two treatment strategies, and the other two trials found more fear of recurrence after MRM than after BCT.

The EORTC Breast Cancer Cooperative Group initiated a prospective, randomized, multicentre clinical trial comparing mastectomy with BCT in patients with stage I and II breast cancer[28]. In this trial HRQoL was assessed as well as survival duration and local recurrence rates. The focus was mainly on body image, fear of recurrence, satisfaction with treatment and cosmetic results, the last elicited from both patients and clinicians. A brief HRQoL questionnaire consisting of two multi-item scales (body image and fear of recurrence) and two single items (satisfaction with treatment and cosmetic result) was included in this trial. HRQoL was evaluated 2 years after the completion of therapy. Significant benefit in body image and satisfaction with treatment was observed in the BCT group. No significant difference was observed in fear of recurrence between the two groups. Ratings of cosmetic results decreased with time, in line with clinical observations of long-term side-effects of radiotherapy. Wide excision appeared to be the most important predictive factor for poor cosmetic result. Poulsen *et al.*[29] have also concluded that patients treated with BCT retain a better body image than those treated with mastectomy.

Whelan *et al.*[30] conducted a randomized trial to evaluate the effects of radiation therapy on HRQoL. Women with lymph node-negative breast cancer who had undergone lumpectomy and axillary lymph node dissection (ALND) were randomized to either breast irradiation or no further treatment. The results demonstrated that radiation therapy had an effect on HRQoL during treatment. After completion of treatment, irradiated patients reported increased breast symptoms (skin irritation, breast pain, upset by the appearance of the breast) compared with non-irradiated patients. However, no significant difference was detected between the groups at 2 years.

One of the impetuses for sentinel node biopsy or selective ALND is the assumed decreased incidence of lymphoedema compared with standard ALND. Velanovich and Szymanski[31] have studied the incidence and effect on HRQoL of postoperative lymphoedema in patients with breast cancer using the SF-36, a generic, well validated instrument. Patients were divided into three groups: breast surgery without ALND, breast surgery with ALND but no lymphoedema, and breast surgery with ALND and lymphoedema. They found that the overall incidence of clinically apparent lymphoedema for both MRM and lumpectomy with ALND is 8·3 per cent. The group with lymphoedema had significantly lower scores in the domains of role-emotional and bodily pain. Even though many patients with lymphoedema appeared to function well, a statistically higher percentage had HRQoL scores below one standard deviation of the national norm in the domains of bodily pain, mental health and general health. So, when lymphoedema occurs, it may cause a demonstrable diminution in HRQoL. It seems clear that efforts to reduce the incidence of lymphoedema, such as sentinel node biopsy, would benefit patients with breast cancer.

Quality of life after treatment of gastric cancer

There are few prospective studies on HRQoL after gastrectomy for gastric carcinoma. The long-term impact on HRQoL of different reconstructive techniques is still a matter of controversy. The results of HRQoL can be biased not only by the method but also by the scorer. This may be the main reason why the results of some studies on the extent of gastric resection or the type of intestinal reconstruction are sometimes controversial[32].

Svedlund *et al.*[33] conducted a prospective randomized clinical trial to determine the impact of various gastrectomy procedures on HRQoL during a 5-year follow-up. Patients eligible for curative gastric cancer surgery were randomized to have either total or subtotal gastrectomy, or a jejunal S-shaped pouch as a gastric substitute after total gastrectomy[34]. Assessment of HRQoL was made on seven occasions during the 5-year follow-up. All patients were interviewed and graded by one of two psychiatrists who rated symptoms and introduced standardized self-report instruments covering both general and specific aspects of life. Using scoring systems known to be able to detect subtle differences, the following may be concluded. Patients who had a total gastrectomy continued to suffer from alimentary symptoms, especially indigestion and diarrhoea, during the entire follow-up period. However, those who had a subtotal gastrectomy had a significantly better outcome even during the first postoperative year. The early results showed that a pouch reconstruction did not improve HRQoL[35]. However, during the course of long-term follow-up significant differences emerged in favour of a gastric reservoir after total gastrectomy. Patients with a gastric substitute improved with the passage of time and had an even better outcome in the long term as they experienced a continued weight gain. Probably both the reservoir function of the pouch and changes in intestinal transit time are important[36]. Similar results were found in a study by Liedman *et al.*[37] who also investigated the effect of a gastric reservoir on weight control. When a subtotal gastrectomy is feasible, this procedure has advantages in the early postoperative period. Pouch reconstruction after a total gastrectomy should be considered in patients with a favourable tumour status suggesting a fair chance of long-term survival.

Thybusch-Bernhardt *et al.*[38] have used the EORTC QLQ-C30 and a validated gastric cancer module[39] to evaluate the effect of radical surgical procedures such as extensive lymph node resection (retrospectively). They concluded that radical gastrectomy combined with D_2 lymphadenectomy does not negatively influence global HRQoL.

Quality of life after treatment of limb sarcoma

Treatment strategies for primary soft tissue sarcoma have emphasized local control with maintenance of limb function, overall survival and HRQoL. External-beam radiotherapy has been widely advocated as a means of improving local control after limb-sparing procedures, although its effectiveness in this role has never been determined definitively. Radiotherapy to the extremity can result in significant functional impairment, such as oedema and wound problems. So, in addition to its effectiveness, it is also important to assess the impact of adjuvant radiotherapy on long-term function and HRQoL. Yang *et al.*[40] performed a randomized prospective study to assess the impact of postoperative external-beam radiotherapy on local recurrence, overall survival and HRQoL after limb-sparing resection of extremity sarcomas. For the analysis, data over a follow-up period of 36 months after surgery were used. In this trial radiotherapy was shown to result in a statistically significant reduction in local recurrence in patients with either high-grade or low-grade sarcoma. However, overall survival and non-local recurrences were nearly identical for patients receiving or not receiving radiation. As a group, those receiving radiotherapy had significantly decreased joint motion in the affected limb compared with those not given radiotherapy. More oedema was found in the treatment group during the first year after surgery; muscle strength was also lower 1 year after surgery. Despite these findings, there were no significant differences between patients in the two treatment arms as measured by a global HRQoL scale (Functional Living Index – Cancer) or in performance of activities of daily living. This study indicates that although postoperative external-beam radiotherapy is highly effective in preventing local recurrence, selected patients with extremity soft tissue sarcoma who have a low risk of local recurrence may not require adjuvant radiotherapy after limb-sparing surgery. Another study showed that use of radiotherapy is a prognostic factor for poor limb function. Again, despite significant objective loss of range of movement and muscle power, patients retained a good HRQoL following limb-conserving therapy[41].

Quality of life after treatment of pancreatic cancer

During the period 1980–1996 there was a 25-fold increase in the number of references in the English language literature to HRQoL in pancreatic cancer; however, only a small proportion report HRQoL assessment during clinical trials. Of 78 papers reviewed by Fitzsimmons and Johnson[42] only nine used a previously validated HRQoL questionnaire and there are inconsistencies in the methods used to collect HRQoL assessment.

The Gastrointestinal Quality of Life Index (GIQLI), a disease-specific questionnaire, is one of the validated questionnaires for patients suffering from different gastrointestinal diseases[43]. Van Dijkum *et al.*[44] have validated the GIQLI for patients with potentially operable periampullary cancer, before surgical treatment. Furthermore, this study demonstrated that the GIQLI could be divided into four subscales, measuring physical well-being, mental well-being, digestion and defaecation. Measuring different aspects of HRQoL allows insight into the different problems affecting a patient at the time of presentation.

Recently, another disease-specific HRQoL questionnaire has become available, the EORTC QLQ-PAN26. Again, this module is intended to supplement the core cancer module (the QLQ-C30). It comprises a number of key symptoms and functional and psychosocial domains. The reliability, validity and clinical responsiveness appear to be good[45]. McLeod *et al.*[46] have described HRQoL after a Whipple procedure. One of the instruments used was the GIQLI, the results of which were presented as a single score. They concluded that HRQoL of patients after a Whipple procedure is excellent.

Quality of life after treatment of oesophageal cancer

The optimum treatment of patients with oesophageal cancer remains controversial. Few studies have prospectively assessed HRQoL using validated instruments. Examples of such instruments are the EORTC QLQ-C30 (a generic instrument) and the Spitzer Index. The latter is performed by a psychologist after an interview. The agreement between doctor and patient, however, appears to be poor[47]. Furthermore, a disease-specific module, QLQ-OES 24, has become available to improve the sensitivity and specifity of the core questionnaire.

Blazeby *et al.*[48] assessed the impact of oesophagectomy and palliative treatment on short- and long-term HRQoL in patients with oesophageal carcinoma using the EORTC QLQ-C30 and the dysphagia scale from the oesophageal cancer module[49]. The conclusion of this longitudinal study is that oesophagectomy has a negative impact on HRQoL. This effect is transient for patients who survive for 2 years or more; however, patients who die within 2 years experience an irreversible diminishment in HRQoL, apart from the relief of dysphagia. Patients selected for palliative treatment initially have a poorer HRQoL than those selected for surgical treatment. After palliative treatment, HRQoL appears to be similar to that of patients who die within 2 years of surgery.

Another prospective study showed that HRQoL after oesophagectomy is impaired primarily by physical limitations and disease symptoms. Two validated instruments have been used, the EORTC questionnaire and the Spitzer Index. The authors conclude that most areas of HRQoL improve with time[47]. However, they excluded patients with recurrence or complications from analysis and the follow-up was short (less than 12 months). These findings should be considered when selecting patients for surgery.

Discussion

It is possible to establish criteria against which HRQoL instruments may be evaluated. HRQoL is a subjective endpoint, so its measurement must include the patient's perspective and be sensitive to change over time. The instrument chosen must be reliable and valid. In addition, practical issues, such as timing of administration, responsibilities for quality control and data management, are particularly important to arrive at valuable data. There is no HRQoL instrument that fits all the above conditions and is suitable in all clinical situations. The choice of instrument cannot be separated from the goals of the study. In the past, results of surgery were measured predominantly in terms of death, disability or cure. HRQoL is already recognized and established in oncology; its implementation in cancer surgery has not yet been completed.

The awareness of HRQoL as an outcome measure in surgery may guide the surgeon in selecting the most appropriate operation. This applies even more when confronted with palliative care, a circumstance in which HRQoL should be regarded as the primary outcome of interest. As a result of the advance of technology, the possibility of surgical intervention tends to increase; the application of such surgical capability seems only justified, however, when satisfactory HRQoL is taken into account as outcome measure. This requires a better understanding and implementation of HRQoL measurement during clinical studies of surgical procedures. The instruments used in these studies should be valid, reliable and sensitive to change. To be able to draw conclusions, the results of HRQoL assessment need to be interpreted. In the absence of guidelines for interpreting clinical meaning, statistical significance is often used as the criterion. The P value is often quoted without reference to the size of the observed effect. The real issue, however, is whether the observed effect is larger than the smallest clinically important effect. These considerations should be kept in mind when investigating HRQoL in surgical oncology.

Several future developments in the area of HRQoL may be predicted. New approaches are now being developed to reduce the number of items that the patient has to answer by applying multimedia devices in an interactive approach (adaptive testing). Standard HRQoL instruments are based on a fixed set of items. The adaptive testing approach improves the reliability of the measurements and reduces the number of items asked of the patient. From a large pool of items, only those that are informative are offered to the patient. This interactive approach stems from intelligence testing. Another approach that may be profitable is the Quality-adjusted Time Without Symptoms of Disease and Toxicity of Treatment (Q-TWIST) method. Originally designed to incorporate aspects of HRQoL into adjuvant chemotherapy, the methodology has also been useful in other disease settings, such as acquired immune deficiency syndrome, rectal cancer and malignant melanoma. The object of the Q-TWIST method is to include survival and HRQoL in a single analysis. These new developments in HRQoL should enhance the use of this type of outcome measure in the clinical situation.

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Randomized clinical trial

Cost–utility analysis of open *versus* laparoscopic groin hernia repair: results from a multicentre randomized clinical trial

Medical Research Council Laparoscopic Groin Hernia Trial Group

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Background: This study was a pragmatic economic evaluation carried out alongside a multicentre randomized controlled trial comparing laparoscopic with open groin hernia repair. The primary economic evaluation framework employed was a cost–utility analysis.

Methods: At 26 hospitals in the UK and Ireland, 928 patients with a groin hernia were assigned randomly to laparoscopic or open repair. Cost data were identified and measured both within and outwith the trial. Cost data were combined with quality-adjusted life years (QALYs) from the EQ-5D questionnaire to obtain cost-per-QALY ratios.

Results: The mean cost of laparoscopic hernia repair was £1112·64, compared with £788·79 for the open operation. The extra cost of £323·85 in the laparoscopic group was mainly due to additional theatre time and increased equipment and sterilization costs. The estimated incremental cost per QALY of the laparoscopic over the open method was £55 548·00 (95 per cent confidence interval £47 216·00–£63 885·00).

Conclusion: While the results show that a high cost was incurred to produce an additional QALY by using laparoscopic over open hernia repair, sensitivity analyses show that there are specific situations in which laparoscopic repair may be a viable alternative, such as when reusable equipment is employed.

Paper accepted 7 January 2001

British Journal of Surgery 2001, 88, 653–661

Introduction

Recent interest in surgery for the repair of groin hernia, and more particularly laparoscopic repair, has been shown by publication of a review of effectiveness[1], as well as its selection as a topic of interest by the National Institute for Clinical Excellence. Although essential, data on effectiveness alone cannot be used to decide surgical policy. Economic evaluation is also required for deciding the place of laparoscopic inguinal hernia repair in health services. The consideration of cost-effectiveness becomes even more important when there is no clear evidence of the predominance of any particular technique, as has been shown by previous research comparing methods of hernia repair[1].

A number of recent trials have included comparisons of the costs and benefits of laparoscopic repair with open repair[2–7]. The economic evaluation reported here was designed alongside a multicentre randomized clinical trial (RCT) to evaluate laparoscopic compared with open inguinal hernia repair, details of which are published elsewhere[8]. This paper adds to existing evidence with the inclusion of a generic outcome measure, EQ-5D[9], from which quality-adjusted life years (QALYs) can be estimated. Since the QALY is a general measure of quality of life (QOL), its use in this study is an attempt to capture specific health outcomes within one overall measure, providing a summary index of the impact of each technique on overall QOL. The inclusion of a generic measure in this economic evaluation is an attempt to provide information for policymakers on the value of the different types of hernia repair.

The multicentre, pragmatic nature of the economic analysis facilitated the capture of normal practice variation thus permitting the reporting of policy-relevant cost estimates. By relating the costs of each type of surgery to any benefits arising, a judgement can be made as to whether any additional benefits of the laparoscopic repair are worth the extra costs.

Patients and methods

Design

This economic evaluation was part of a RCT of laparoscopic *versus* open groin hernia repair. At 26 hospitals in the UK and Ireland, 928 patients with a groin hernia were randomly assigned to laparoscopic (n = 468) or open (n = 460) hernia repair. Patients were recruited between January 1994 and March 1997. All patients with an inguinal or femoral hernia were eligible unless they were medically unfit for anaesthesia, had a previous midline or paramedian incision, an incarcerated or inguinoscrotal hernia, an uncorrected coagulation disorder, or were pregnant. Laparoscopic repair was performed using either a transabdominal preperitoneal or a totally extraperitoneal approach, depending on the surgeon's preference. The method of open repair was decided pragmatically by each individual surgeon; most used tension-free mesh repair. A detailed description of the RCT and the main outcomes is reported elsewhere[8]. The economic evaluation framework used in this study was a cost–utility analysis carried out from a health service perspective. However, the paper also relates costs to other outcomes, such as time taken to return to usual activities.

Measurement of costs

Data on duration of operation, staffing and postoperative hospital stay for all trial patients were collected prospectively on standard forms to record preoperative, operative and postoperative indices. Questionnaires were also sent to all participants at 3 months and 1 year after the operation. (Copies of questionnaires can be obtained from the authors.)

Operative costs

Theatre running costs were identified from each centre by obtaining estimates of the booked cost of a theatre hour, which reflected fixed and semifixed costs. This was then combined with variable operative costs. To obtain the most accurate data and to capture specific details of variation between centres as well as ranges for resource use, operative costs relating to groin hernia repair (equipment, consumables and sterilization) were identified and measured prospectively. A structured questionnaire was completed during a sample of operations from the main centres covering all types of practice. For items of equipment, an estimate of their lifespan was obtained as well as an approximation of the number of times used. From this, an annual equivalent cost was estimated and divided by the annual use to obtain a cost per patient. The staffing element of theatre costs was based on each theatre's specific 'team', reflecting the grade of surgeon and assistant, as well as the number and grade of nursing staff. Where operative complications were identified from the trial data, clinicians assisted in compiling the costs of each event. These additional resources were attached to the respective patient's costs as a 'complication cost'. For each recurrent hernia identified from trial data, costs were assessed from a case-note review, based on available centre data on each type of operation, as described above.

Other healthcare costs

The specific cost of an inpatient day (including staffing, capital charges and overheads) on a general surgical ward was established at each centre. Where such marginal cost data were not available, the less specific mean cost per day at the centre was purged of elements already costed in the trial, such as staffing, equipment and supplies. For each patient, this cost was multiplied by the total inpatient stay obtained from trial data. Postoperative complications requiring additional resources were also identified from trial data and costed accordingly. Drugs were costed according to manufacturers' price lists[10].

Mean costs for the laparoscopic and open hernia groups were calculated using individual patient data refined with the additional, more detailed information from the operative cost questionnaire. The cost data were analysed by intention to treat. Length of hospital stay was analysed by the Mann–Whitney U test and return to usual daily activities was analysed by Kaplan–Meier survival analysis and the log rank test. Differences between the means of the two groups were calculated for each cost outcome. Confidence intervals were calculated for the total cost variable.

Items of resource use were measured and valued in their naturally occurring units, e.g. per ampoule of drug or hour of staff time. Valuation was carried out at 1998 prices, using financial data from each centre augmented with unit cost data from the various laparoscopic equipment suppliers and available literature sources[10–12] and, where appropriate, annuitized using a 6 per cent discount rate[13], according to lifespan and use. The study lasted 12 months; however, potential future costs, such as those associated with recurrent hernias, were discounted and overheads and capital charges were allocated accordingly to the hospital in use. The data were analysed using Microsoft Excel©[14] and the statistical package SPSS©[15]. Sensitivity and threshold analyses were performed and are reported in this paper. For a more detailed account of the design and methodology used in this study, readers are referred to McIntosh *et al.*[16].

Health status

The primary clinical endpoints are reported elsewhere[8]. They include: complications, return to usual social activities, hernia recurrence and groin pain persisting at 1 year. The EQ-5D questionnaire[9] was included for the economic evaluation to permit the calculation of QALYs. These data were obtained at three time points: 1 week, 1 month and 3 months after the operation. The EQ-5D is a generic measure of health status that defines health in terms of five broad dimensions, each with three levels (*Table 1*). Combinations of these dimensions and levels gives rise to 243 health states. These health states were given QOL scores by a sample of the general public and a UK tariff compiled[17]. For each patient, EQ-5D responses to each of the five dimensions were scored by multiplying the valuation of their health state by the duration of time spent in that state. Since only three time points of EQ-5D data were available, power curves were fitted to model the EQ-5D profiles for the laparoscopic and open hernia repair groups over the period from baseline to 3 months. Essentially this means that a difference in QOL was assumed to exist for 3 months but with the magnitude of difference diminishing over time, from a maximum at 1 week to zero at 3 months. In addition, QALYs lost due to recurrence in the laparoscopic group were netted out from this QALY gain. Again, a power curve was fitted for the recurrent hernia operations whereby it was assumed that if patients had not had a recurrence they would have returned to a predicted health state. The mean QALY gain/loss was combined with costs to produce an incremental cost per QALY for laparoscopic repair.

Table 1 The EQ-5D descriptive system

Mobility	
1	No problems in walking about
2	Some problems in walking about
3	Confined to bed
Self-care	
1	No problems with self-care
2	Some problems washing or dressing self
3	Unable to wash or dress self
Usual activities	
1	No problems with performing usual activities (e.g. work, study, housework, family or leisure activities)
2	Some problems with performing usual activities
3	Unable to perform usual activities
Pain/discomfort	
1	No pain or discomfort
2	Moderate pain or discomfort
3	Extreme pain or discomfort
Anxiety/depression	
1	Not anxious or depressed
2	Moderately anxious or depressed
3	Extremely anxious or depressed

From reference 17

Results

Data from the operative questionnaires showed minimal variation in resources used between centres for open repairs. However, there were large variations in resource use between laparoscopic repairs mainly resulting from varying equipment and sterilization practices. Some of the variation in the laparoscopic procedure was a result of specific individual hospital policy on reusable or disposable equipment, reduced options because of limited resources, or reflected the use of free or discounted tester goods from suppliers promoting laparoscopic equipment.

The range of the costs collected during the trial is shown in *Table 2*. The mean cost of laparoscopic hernia repair was £1112·64, compared with £788·79 for the open operation (*Table 3*). The extra cost of £323·85 (95 per cent confidence interval in mean difference £275·27 – £372·45) in the laparoscopic group was due to additional theatre running costs, increased equipment use and more expensive instrument sterilization. Postoperative costs such as general practitioner appointments, hospital outpatient appointments and other appointments after laparoscopic repair were £114·49, compared with £99·00 in the open group. There were seven recurrences after laparoscopic repair compared with none after open repair, a statistically significant difference[8]. This represented a mean 'recurrence' cost of £6·57 after laparoscopic repair.

Quality-adjusted life years

There was a difference in the EQ-5D weights at 1 week after operation (*Table 4*); the utility score was significantly higher in the laparoscopic group, 0·74 *versus* 0·68. The difference between the groups converged at 3 months. Since only three time points were available, power curves were fitted to these data; this gave rise to a gain in QALYs in the laparoscopic group of 0·00614 per person. A power curve was fitted for the recurrent hernia operations, whereby it was assumed that if patients had not had a recurrence they would have returned to a health state of 0·86 (as reflected by the 3-month state shown in *Table 4*). This gave rise to a mean loss in QALYs of 0·00031, so the overall mean gain in QALYs for the laparoscopic group was 0·00583. The estimated incremental cost per QALY, or the *extra* cost per *extra* QALY gained in moving from open to laparoscopic repair was £55 548·00 (£323·85/0·00583) (95 per cent confidence interval £47 216·00 – £63 885·00).

Table 2 Selection of costs of resources used in laparoscopic and open hernia repairs (1998 prices)

Resource	Approach	Unit cost
Staff		
Consultant	L/O	£35·36 per h
Senior registrar	L/O	£18·66 per h
Staff nurse	L/O	£8·89 per h
Theatre time	L/O	£197·34 per h
Pharmacological agents		
Temazepam*	L/O	£0·04 (13 mg)
Voltarol*	L/O	£0·98 (75 mg)
Lignocaine 1 per cent*	L/O	£0·25 (2-ml ampoule)
Muscle relaxant (vecuronium*)	L	£4·44 (10 mg)
Reversal agents (glycopyrronium bromide and neostigmine*)	L	£0·56 (ampoule)
Prophylactic antibiotics	L/O	£6·22 (1·5-g vial)
Morphine*	L/O	£0·75 (10-mg ampoule)
Anaesthetic equipment		
Laryngeal mask	O	£2·26 (Disposable)
T piece (oxygen)	O	£0·41 (Disposable)
Endotracheal tube	L	£1·37 (Disposable)
Yankauer suction	L	£0·36 (Disposable)
Hudson mask (oxygen mask)	L	£0·41 (Disposable)
Operating equipment		
Endoscopy system (camera and light source)	L	£18 820·39 (Capital cost)
Video unit	L	£1 298·38 (Capital cost)
TV monitor(s)	L	£1 208·75 (Capital cost)
Endoscope (0°)	L	£2 325·33 (Capital cost)
Insufflator (CO_2)	L	£6 308·33 (Capital cost)
Reusable instruments		
Grasper	L	£505·35 (Capital cost)
Scissors	L	£533·83 (Capital cost)
Dissector	L	£533·83 (Capital cost)
Basic instrument tray	L/O	£1 069·16 (Capital cost)
Equipment maintenance contracts	L/O	Negotiable
Sterilization		
Autoclave	L/O	£17 625 (Capital cost)
Ultrasonic machine	L	£2 162 (Capital cost)
Fluid	L/O	£25·85 per day
Basic tray reprocessing	L/O	£28·32 per tray
Marginal cost of an inpatient day	L/O	£202·10
Follow-up appointments		
General practitioner	L/O	£14
Outpatient appointment	L/O	£62·04

*Reference 10. L, laparoscopic; O, open

Sensitivity analysis

Reusable versus *disposable equipment*

One of the major differences between the centres in this study affecting costs was the different types of laparoscopic equipment used. The laparoscopic cost reported in *Table 3* is a mean value reflecting variation between the centres. The policy of employing reusable equipment reduced the mean operative cost of the laparoscopic procedure from £998·15 to £817·79, a fall of £180·36, the total cost reducing from £1112·64 to £932·28 (*Table 5*). This narrowed the difference between laparoscopic and open repairs to £143·49 (£932·28 *versus* £788·79). Combining this with the postoperative and appointment costs, use of reusable equipment would give an incremental cost per QALY in moving from open to laparoscopic surgery of £24 612·00 ((£932·28 – £788·79)/0·00583). The increased operative costs of laparoscopic surgery using disposable equipment were £1294·18 *versus* £696·96. Combining this with the postoperative and appointment costs, use of disposable equipment would give

Table 3 Mean cost of laparoscopic and open hernia repairs per patient

Cost variable	Laparoscopic (£)	Open (£)	Difference in means (£)
Operative costs			
Theatre running costs*	300·28	218·83	81·45
Perioperative drugs	14·50	11·37	3·13
Equipment costs†	230·58	13·34	217·24
Sterilization costs	41·10	28·38	12·72
Hospital stay	383·64	385·27	−1·63
Theatre consumables	23·97	32·57	−8·60
Complication costs	4·08	0·03	4·05
Total operative costs	998·15	689·79	308·36 (259·18–357·53)
Postoperative and appointment costs			
Postoperative drugs	0·71	0·98	−0·27
Postdischarge analgesics	0·41	0·47	−0·06
Recurrence cost	6·57	0	6·57
GP appointments	10·50	12·92	−2·42
Hospital outpatient appointments	94·11	83·63	10·48
Other appointments	2·19	1·00	1·19
Total postoperative and appointment costs	114·49	99·00	15·49
Overall cost	1112·64	788·79	323·85 (275·27–372·45)

Values in parentheses are 95 per cent confidence intervals. Costs reported in 1998 prices. *Includes staff, administration and overheads; †includes disposable equipment used in the laparoscopic group. GP, general practitioner

Table 4 Scores obtained from the outcome measure EQ-5D 1 week, 1 month and 3 months after operation

	Laparoscopic repair	Open repair	*P*
1 week			
No. of patients	308	302	
EQ-5D utility score	0·74(0·24)	0·68(0·24)	0·003
1 month			
No. of patients	249	246	
EQ-5D utility score	0·82(0·23)	0·79(0·22)	0·12
3 months			
No. of patients	261	236	
EQ-5D utility score	0·85(0·22)	0·86(0·20)	0·80

Values are mean(s.d.). *t* test

an incremental cost per QALY in moving from open to laparoscopic repair of £102 439·00 ((£1294·18 − £696·96)/0·00583).

Operating time

The operation took 15 min longer in the laparoscopic group: mean(s.d.) 58·4(22·5) *versus* 43·4(15·9) min. Threshold analysis was used to calculate the reduction in operating time that would have to be achieved for the laparoscopic procedure to break even with the costs of the open repair (*Fig. 1*). An operating time of 34 min is the threshold at which laparoscopic repair is equivalent in cost to open hernia repair.

Length of stay

The median (interquartile range (IQR)) length of stay after laparoscopic and conventional hernia repairs was

Table 5 Sensitivity analysis on total operative costs

	Laparoscopic repair (£)	Open repair (£)
Reusable laparoscopic equipment	817·79 (785·56–850·02)	685·59 (663·33–707·75)
Disposable laparoscopic equipment	1294·18 (1258·49–1329·87)	696·96 (673·38–720·54)
Length of stay in open repair group increased by 1 day	998·15 (954·45–1041·85)	854·15 (827·98–880·32)

Values are mean (95 per cent confidence intervals). See *Table 2* for a description of total operative costs. *Mean costs in non-varying group may change slightly on sensitivity analysis due to statistical estimation by intention to treat reported previously as 1 (1–1) and 1 (1–2) days respectively[8]. Since the IQR for open repair extended to 2 days, the sensitivity of the cost estimated to this variation was examined. The total operative costs for open repair increased to £854·15 (*Table 5*), reducing the difference from £323·85 to £159·49 (£1112·64 – £953·15. Based on this sensitivity analysis, the incremental cost per QALY in moving from open to laparoscopic repair decreases from £55 552·00 to £27 357·00 ((£1112·64 – £953·15)/0·00583). Open and laparoscopic procedures can also be carried out as a day case. While this trial did not compare these options, the data showed no significant difference between length of stay. Hence the cost difference was not driven by this factor. As a result, the actual difference in cost reported would probably be unaffected if the interventions had been carried out as a day case.

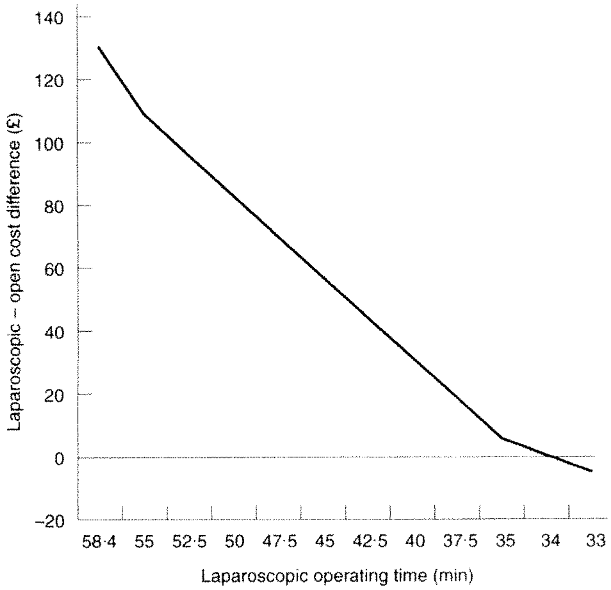

Fig. 1 Threshold analysis: break even point for laparoscopic surgery with reusable equipment compared with open repair

Combining cost data with other clinical outcomes

A summary of the clinical outcomes, as published previously[8], is provided in *Tables 6* and *7*. Using data on 'Usual activities' as the sole outcome, patients in the laparoscopic group were able to enjoy usual social life after a mean of 10 days while those in the open group were not able to enjoy usual social life until 14 days after operation, a statistically significant difference of 4 days ($P = 0{\cdot}01$). Using the cost data, this equates to an extra cost of £80·97 per extra day's gain in usual social activities (£323·85/4). Using the cost data with the outcome 'Able to enjoy usual interests or hobbies', the laparoscopic group returned to these activities 7 days earlier. Thus, the cost of an extra day's gain in usual interests or hobbies was £46·26 (£323·85/7).

Table 6 Return to usual activities

	Laparoscopic repair		Open repair		
	*n**	Time to return of activities (days)	*n**	Time to return of activities (days)	*P*
Able to enjoy usual social life	314	10 (7–21)	276	14 (7–28)	0·010
Able to enjoy usual interests or hobbies	284	14 (10–30)	254	21 (10–42)	0·049
Return to paid employment	162	28 (14–42)	153	42 (21–61)	0·001

Values are mean (range). *Number of patients for whom return to particular activity is applicable. Kaplan–Meier analysis and log rank test

Table 7 Clinical outcomes 1 year after operation

	Laparoscopic repair* (*n* = 394)	Open repair* (*n* = 362)	Difference in percentages†	*P*
Any pain in groin in last week?	113 (28·7)	133 (36·7)	– 8·1 (14·7 to –1·4)	0·005
Recurrence of hernia	7 (1·9)	0 (0)	1·9 (0·5 to 3·4)	0·001

*Values in parentheses are percentages; †values in parentheses are 95 per cent confidence interval

Discussion

The mean cost of laparoscopic hernia repair was £1112·64, compared with £788·79 for the open operation. The difference of £323·85 was very similar to the £335·00 difference reported in the most recent economic evaluation of laparoscopic *versus* open mesh repair[7]. The difference in cost reported in Lawrence *et al.*[4] was £583·00. This higher cost difference is a reflection of the greater use of expensive disposable equipment and longer operating times for laparoscopic hernia repair (72 min). The reduced difference reported in this study reflects the current practice variation among surgeons, typified by an increased use of reusable equipment, as well as reduced operating times for laparoscopic repair (58 min).

For practical reasons, many economic evaluations in hernia repair have collected data at a small number of centres: one[18,19], two[4,7], or three[5]. A multicentre trial generally has greater external validity[20]. A greater number of centres allows for variation between hospitals such as policies on hospital stay and theatre equipment, and differing policies on the number and type of staff in theatre. In this study more detailed data were collected at the main centres covering a broad geographical spread. Hence, the mean values reported in this study are more likely to reflect common practice variation amongst centres with a mix of fully reusable, fully disposable and mixed disposable/reusable equipment. In this study, sensitivity analysis showed that the mean cost varied markedly when a specific reusable or disposable only scenario was employed; laparoscopic repair with disposable equipment cost almost double that of open hernia repair. Reusable laparoscopic equipment reduced the difference to only £143·49 per patient. Wellwood *et al.*[7] reported similar results, although the cost difference with disposable equipment was less extreme.

In their sensitivity analysis, Lawrence *et al.*[4] showed that when the duration of laparoscopic hernia repair was halved, it remained more expensive, unless open repair incurred a 2-year recurrence rate of at least 15 per cent. Threshold analysis in this study showed that the operating time in the laparoscopic procedure would have to be reduced by 24 min, as well as using reusable equipment, before it was equivalent to open hernia repair in terms of cost. There is a learning curve associated with minimally invasive therapy; the present cost analysis could be seen as comparing open hernia repair performed by experienced surgeons with laparoscopic repair by relatively less experienced surgeons.

Combining the cost data with the EQ-5D data showed the incremental cost per QALY of laparoscopic over open hernia repair was £55 552·00. These cost-per-QALY ratios give an indication of the health gain of offering routine laparoscopic hernia repair and therefore permit consideration of whether resources could be better used elsewhere. The interpretation of QALY gains within league tables, however, should be carried out with caution[21]. There is no explicit policy guidance on acceptable cost-per-QALY figures. However, ballpark implied estimates are that between £15·00 – £20 000·00 per incremental QALY is worthwhile. In a recent published review of studies reporting cost-per-QALY gains[22], the range of incremental cost-per-QALY figures was from £9·00 to £900 000·00 (median £4961·00). These data place the incremental cost-per- QALY of laparoscopic hernia repair in the, relatively high, ninth decile of this range.

The generic QALY may not be sensitive enough to identify differences in surgical outcomes. In this study the laparoscopic hernia repair group reported less persistent groin pain and less numbness in the groin at 1 year, yet the EQ-5D converged at 3 months. Possible reasons include that either the EQ-5D is not sensitive enough, or persistent groin pain and numbness do not influence QOL, or the groups diverged after 3 months (which would not be identified as the EQ-5D was not completed at 1 year).

Using data on 'usual activities' this study showed that people who had laparoscopic hernia repair returned to usual interests or hobbies 7 days earlier than those in the open repair group. Thus the cost to the health service of an extra day's return was £46·26. Further research is required into how patients value the different outcomes[7]. Patients may be prepared to trade attributes such as waiting time or cost for an improvement in QOL and better short-term clinical benefits, favouring the laparoscopic procedure. Conjoint analysis could be used to establish the trade-offs between the attributes of each procedure and provide monetary estimates of benefit or utility scores for both laparoscopic and open hernia repair.

Recently, a number of papers have suggested techniques for stochastic cost-effectiveness analysis[22,23]. However, as yet, there is no agreement as to the preferred method. The present study concentrated on mean costs and mean benefits. The main uncertainty in this study was based on equipment/supplies, i.e. variability between centres. This was overcome by very detailed compilation of specific operative resources at the main centres.

Lawrence *et al.*[4] carried out a sensitivity analysis showing what recurrence rates and costs for open hernia repair would have to be for it to break even with the more expensive laparoscopic costs. In the present study there were seven recurrences in the laparoscopic group. If this variable represented the main outcome and it was compared with costs this would give a clear economic answer – the open operation provides added benefit at a reduced cost. This study has shown an unusually high recurrence rate after laparoscopic repair of 1·9 per cent[8]; despite this, it had little influence on costs and would only do so when unrealistically high rates were reached.

In the main clinical report of the trial[8] concerns about rare, serious complications and hernia recurrence were considered to support restricting the use of laparoscopic repair to specialist surgeons. From an economic perspective these rare events had little influence on costs. Laparoscopic repair would become more cost-effective if surgeons performed the operation more quickly. The two procedures become cost-equivalent if the duration of laparoscopic repair is reduced by 24 min to a mean of 34 min.

A number of studies have included estimates of indirect costs or productivity gains of hernia repair[2,5,18,24]. Kald *et al.*[5] used the human capital approach to estimate indirect costs and concluded that laparoscopic repair was the most cost-effective strategy, provided that both direct and indirect costs were included. Liem *et al.*[2] showed that the inclusion of costs to society offset the additional costs of laparoscopic repair by 75 per cent. The human capital approach is no longer recommended automatically because of theoretical flaws[25] and the inclusion of indirect costs is also controversial. In recently published guidelines, the Washington Panel provided recommendations on how to incorporate productivity costs into cost-effectiveness analysis, using a QALY approach[26]. This approach recommends incorporating productivity costs as *health effects* in the QALY[27]. For these reasons and, as in Wellwood *et al.*[7] and Lawrence *et al.*[4], this study did not calculate indirect costs separately. However, given that patients in the laparoscopic group who were employed returned to work 14 days before patients who had open repair and the added cost of the laparoscopic group was £323·85, an automatic or 'implied' value of each extra day's return to work would be £23·00. By definition, such an implied value does not reflect the value a patient places on early return to work. However, such an approach provides a starting point for valuation without entering the debate on the best way of calculating indirect costs.

In conclusion, the costs of laparoscopic repair were greater than those of open hernia repair. However, there were significant short-term QOL benefits after laparoscopic repair as reflected by the additional QALY gain, although differences were no longer significant after 3 months. Economic evaluation summarizes complex information by providing data on costs on one side and health gain (e.g. QALYs) on the other. Since both costs and health gain were higher in the laparoscopic arm, the judgement is whether an extra QALY obtained by the laparoscopic procedure is 'worth' an extra £55 552·00. The type of information provided in this paper can be used for decision-making purposes between differing specialty budgets, as well as for providing information on the relative cost-effectiveness of different hernia repairs.

Acknowledgements

This study was funded by the Medical Research Council (MRC). The MRC Laparoscopic Groin Hernia Trial Group is grateful to the theatre, nursing and pharmacy staff at each of the centres for help with identifying, measuring and collecting resource use data; to the staff at each of the finance departments and sterilization centres for provision of cost information; and to the many suppliers of laparoscopic equipment for providing cost information on request for each item of equipment used in each operating theatre. The authors are grateful to John Cairns and Luke Vale of the Health Economics Research Unit and Health Services Research Unit, University of Aberdeen, and Mark Sculpher, University of York, for valuable comments on earlier drafts, and to Sue Ross of the Health Services Research Unit. The Health Economics Research Unit and the Health Services Research Units are core funded by the Chief Scientists Office of the Scottish Executive Department of Health. Professor C. Donaldson is a Canadian Institutes of Health Research Senior Investigator and an Alberta Heritage Senior Scholar. The views in this paper are those of the writing committee and not the funders.

The writing committee for this article included Ms E. McIntosh, Health Economics Research Centre, University of Oxford, Professor C. Donaldson, University of Calgary and Health Economics Research Unit, University of Aberdeen, and Mr N. Scott and Professor A. Grant, Health Services Research Unit, University of Aberdeen.

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A list of clinical collaborators and data co-ordinators was published with the clinical results (*Lancet* 1999; **354:** 185–90).

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Randomized, dose-finding phase III study of lithium gamolenate in patients with advanced pancreatic adenocarcinoma

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Background: Chemotherapy for pancreatic cancer offers small survival benefits and considerable side-effects. Unsaturated fatty acids have an antitumour effect in experimental studies; in phase II studies few side-effects were seen.

Methods: In this group-sequential, open-label, randomized study, 278 patients with a diagnosis of inoperable pancreatic cancer were treated with either oral (700 mg daily for 15 days), low-dose (0·28 g/kg) or high-dose (0·84 g/kg) intravenous lithium gamolenate (LiGLA). The primary endpoint was survival time from randomization using Kaplan–Meier estimates.

Results: Median survival after oral and low-dose intravenous treatment was 129 and 121 days respectively. Median survival after high-dose intravenous treatment was 94 days. A good Karnofsky score and the absence of metastases were associated with increased survival. Haemolysis, a marker of rapid infusion, was associated with a median survival time of 249 days in the low-dose intravenous group.

Conclusion: Oral or low-dose intravenous LiGLA led to survival times similar to those of other treatments for pancreatic cancer although one subgroup (low-dose intravenous LiGLA with haemolysis) had longer survival. High-dose intravenous treatment appeared to have an adverse effect. Systemic treatment with LiGLA cannot be recommended for the treatment of pancreatic cancer.

Paper accepted 14 January 2001

British Journal of Surgery 2001, 88, 662–668

Introduction

Pancreatic cancer is the fifth most common cause of cancer-related death in men and the seventh most common cause of cancer-related death in women in the western world, with an estimated incidence of 9–10 cases per 100 000 population[1]. The prognosis is poor; the average survival time after diagnosis is less than 6 months and fewer than 4 per cent of patients survive 5 years[1,2].

Certain polyunsaturated fatty acids (PUFAs), particularly the highly unsaturated fatty acids including gamolenic acid (GLA), have been shown *in vitro* to have antitumour activity. They are cytotoxic to tumour cells at concentrations that show little or no toxicity to normal cells under similar conditions. In addition to producing cell death through the production of peroxides and superoxides during lipid peroxidation, PUFAs may contribute to apoptosis and cell cycle arrest. There is evidence that PUFAs exert a regulatory effect on tumour invasion and metastasis by improving cell–cell adhesion (increasing E-cadherin and desmosomal protein expression and changes in membrane fluidity), reducing tumour cell–matrix adhesion, inhibiting enzymatic matrix degradation and reducing tumour cell motility (spontaneous and motogen mediated)[3].

The partially water-soluble lithium salt of GLA, lithium gamolenate (LiGLA), has been shown to have dose-related selective growth inhibitory and cytotoxic effects on human pancreatic cell lines[4]. Results from a phase II open-label, dose-escalation study of intravenous LiGLA in 48 patients with pancreatic cancer demonstrated an increase in patient survival[5]. Intravenous LiGLA was well tolerated; adverse events were clinically insignificant compared with those associated with chemotherapy[5].

The aim of this study was to compare the efficacy and safety of two intravenous doses of LiGLA with that of oral treatment. The primary endpoint was patient survival. Secondary endpoints included assessment of tumour response and treatment toxicity.

Materials and methods

This group-sequential, open-label, randomized study was conducted at 17 centres between December 1993 and June 1996. Ethics committee approval was obtained in each centre and all patients gave voluntary written informed consent, before enrolment into the study. The study was conducted in accordance with Guidelines on Good Clinical Practice[6] and the principles of the Declaration of Helsinki[7].

Regular independent interim analyses were performed, and reviewed in confidence by an independent review committee. The study was terminated when there was statistical evidence of a difference in survival rate between the treatment groups.

Patients

Two hundred and seventy-eight patients, aged 18–84 years, with a diagnosis of inoperable pancreatic cancer were randomized to receive treatment as described below. Patients were required to have either a histological diagnosis of pancreatic cancer or an unequivocal clinical and radiological diagnosis, a predicted survival time of at least 2 months and a Karnofsky performance status of at least 60 per cent. In addition, at some time within a month of entry to the study, patients had to have a serum albumin level greater than 30 g/l.

Randomization was carried out at a central registry; patients were allocated to treatments by minimization to ensure a balance between groups for sex, age, presence of distant metastases and previous chemotherapy and/or radiotherapy.

Study assessments

All prestudy screening (baseline) assessments were performed no more than 4 weeks before the start of treatment. Diagnosis was confirmed by computed tomography (CT) and/or ultrasonography, staging of the disease and histology where available. Karnofsky performance status was assessed and medical history and other demographic data were recorded. Blood samples were collected for the measurement of serum lithium levels, and for biochemical and haematological assessment.

At weeks 6, 10, 14, 30 and 42 after starting treatment, and at 12-week intervals thereafter, the patients were assessed clinically, the Karnofsky performance status was noted, and blood was taken for biochemical and haematological analysis. Adverse events and concomitant medication were recorded on the first and last day of each treatment interval, and on day 7 of each treatment interval in patients receiving intravenous therapy. Patients receiving intravenous treatment were monitored daily by dipstick urinalysis for haemolysis or haemoglobinuria. Serum lithium levels were measured in all patients receiving intravenous treatment on days 2, 4 and all subsequent days of the treatment, and in orally treated patients on the last treatment day only.

Tumour response was assessed by CT and/or ultrasonography at week 6, week 30 and at alternate visits thereafter. Scans of patients in whom the disease was considered to have stabilized or improved were reviewed independently.

Patients were followed until death or termination of the study.

Treatments

LiGLA was supplied by Scotia Pharmaceuticals (Stirling, UK). Oral medication was provided as gelatin capsules, containing 350 mg GLA as the lithium salt. Patients were required to take two capsules (700 mg) each day for 15 days. Intravenous medication was provided as 5-ml ampoules containing 140 mg/ml LiGLA (equivalent to 700 mg GLA) in 12 per cent aqueous ethanol. This was diluted in 500 ml 0·9 per cent sterile saline and 10 000 units heparin and administered by slow intravenous infusion. Patients with a previous history of thromboembolic disease were pre-treated with an additional 10 000 units heparin before commencing treatment with intravenous LiGLA. Treatment commenced with one ampoule on day 1, followed by increasing daily doses until a total dose of either 0·28 g per kg body-weight (low dose) or 0·84 g per kg body-weight (high dose) had been infused over 10–12 days. Serum lithium levels were measured and the rate of infusion was reduced or treatment interrupted if the serum lithium level rose above 0·7 mmol/l.

All patients started treatment within 4 weeks of the screening/baseline visit. A further course of treatment could be given at the discretion of the responsible clinician 24 weeks after the first course and at 6-month intervals thereafter.

Statistical analysis

The study was designed to have 90 per cent power to detect a difference in median survival of 4 months between the oral and high-dose intravenous treatment groups at a 5 per cent level of significance. The reference median for oral treatment was taken to be 120 days.

Table 1 Patient characteristics at entry to the study

		LiGLA treatment group		
	All (*n* = 278)	Oral (*n* = 93)	Low intravenous (*n* = 90)	High intravenous (*n* = 95)
Histologically confirmed disease	163 (59)	57 (61)	53 (59)	53 (56)
Metastatic disease				
No distant metastasis	157 (56)	54 (58)	51 (57)	52 (55)
Distant metastasis	119 (43)	39 (42)	38 (42)	42 (44)
Not assessed	2 (1)	0 (0)	1 (1)	1 (1)
Previous treatment				
Chemotherapy only	19 (7)	9 (10)	4 (4)	6 (6)
Radiotherapy only	10 (4)	4 (4)	1 (1)	5 (5)
Chemotherapy and radiotherapy	22 (8)	9 (10)	5 (6)	8 (8)
Karnofsky performance status (%)				
60	17 (6)	7 (8)	5 (6)	5 (5)
70–80	132 (47)	51 (55)	43 (48)	38 (40)
90–100	126 (45)	35 (38)	40 (44)	51 (54)
Not assessed	3 (1)	0 (0)	2 (2)	1 (1)
Jaundice at prestudy assessment	96 (35)	25 (27)	33 (37)	38 (40)*

Values in parentheses are percentages. LiGLA, lithium gamolenate. *χ^2 = 48·2, 2 d.f., $P < 0·01$

Table 2 Reasons why patients were withdrawn from the study

		LiGLA treatment group		
	Total (*n* = 278)	Oral (*n* = 93)	Low intravenous (*n* = 90)	High intravenous (*n* = 95)
Death				
From pancreatic cancer	146	46	51	49
Other causes	13	7	3	3
Adverse event	6	2	0	4
Request of patient	28	8	10	10
Withdrawn by investigator	36	8	12	16
Lost to follow-up	6	3	2	1
Other reason (details not recorded)	9	3	4	2
Alive at study termination	32	16	7	9
Not known	2	0	1	1

LiGLA, lithium gamolenate

The double triangular test[8] was used to compare survival rates at each interim analysis and to enable termination of the study when evidence was sufficient. The primary comparison of survival in the test was between the high-dose intravenous and oral treatments. The first interim analysis was planned after a total of 40 deaths had occurred in these two groups, with subsequent interim analyses after every 30 new deaths in these groups.

Patient survival was estimated from the date of randomization (primary efficacy variable), and from the date of first treatment and the date of diagnosis (secondary efficacy variables), for all patients and for all patients with histological confirmation, by the Kaplan–Meier method. Patient survival was also modelled using the Cox proportional hazards model to investigate the effect on survival of various covariates (sex, age, presence or absence of metastases, previous chemotherapy and/or radiotherapy, and Karnofsky performance status) and treatment. Possible interactions between these covariates were also investigated. Terms were included in the statistical model if they were significant at the 10 per cent level. To enable the influence on survival of each factor to be assessed, risk ratios were obtained from the proportional hazards model. A 5 per cent level of significance was used to determine whether a covariate or treatment effect was significant.

Results

The study was terminated by the independent review committee after the fourth interim analysis.

Ninety-three patients received LiGLA 700 mg orally for 15 days, 90 patients received a low-dose intravenous infusion of LiGLA (total dose 0·28 g/kg) and 95 patients received a high-dose intravenous infusion of LiGLA (total dose 0·84 g/kg). The treatment groups were similar in age (mean 63 years), height (mean 168·8 cm) and weight (mean 63·5 kg). Baseline disease characteristics were similar, apart from significant differences in the distribution of jaundice at the time of prestudy assessment (*Table 1*).

Forty-seven patients (17 per cent) received a second course of treatment: 21 patients in the oral group, 18 in the low-dose intravenous group and eight in the high-dose

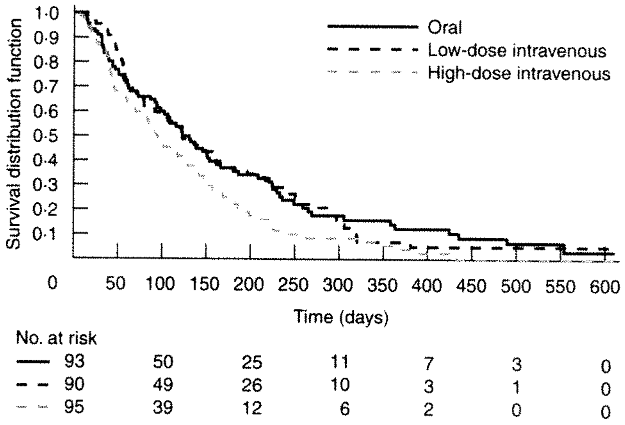

Fig. 1 Kaplan–Meier plots of survival from randomization: 278 patients with pancreatic cancer treated with lithium gamolenate

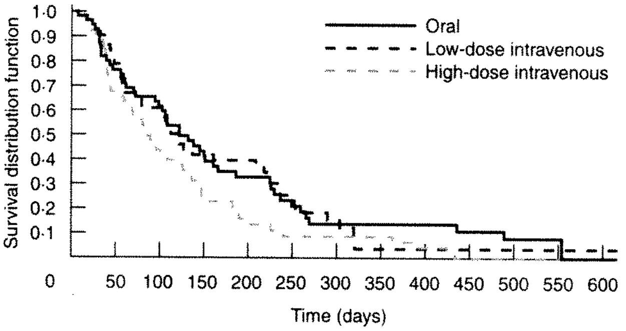

Fig. 2 Kaplan–Meier plots of survival from randomization: 163 patients with histologically confirmed pancreatic cancer treated with lithium gamolenate

Table 3 Risk ratio estimates for survival after randomization of variables tested in the Cox proportional hazards model

	Degrees of freedom	Risk ratio
Karnofsky performance status (%)		
90	1	2·252 (1·322–3·836)
80	1	3·610 (1·050–6·358)
70	1	4·647 (2·657–8·128)
60	1	4·600 (2·217–9·547)
Metastases	1	1·972 (1·494–2·601)
Age (≤ 60 and > 60 years)	1	1·275 (0·947–1·717)
Sex	1	1·051 (0·794–1·391)
Previous treatment	1	1·503 (0·906–2·495)
Low-dose intravenous LiGLA	1	1·019 (0·728–1·426)
High-dose intravenous LiGLA	1	1·919 (1·364–2·699)

Values in parentheses are 95 per cent confidence intervals. LiGLA, lithium gamolenate

intravenous group. Four patients in the oral group and two in the low-dose intravenous group received a third course of treatment and one patient in the low-dose intravenous group received a fourth course of treatment.

At the time of study termination, 32 patients were still in the study; 159 had died, six were withdrawn because of adverse events and the remainder had either been withdrawn by the investigator or were discontinued for other reasons (*Table 2*).

Survival analyses

Kaplan–Meier survival curves from the date of randomization are shown for all patients (*Fig. 1*) and for patients with histologically confirmed pancreatic carcinoma (*Fig. 2*).

Patients in the oral treatment group had a median survival time from randomization of 129 days compared with 121 days for the low-dose intravenous group and 94 days for the high-dose intravenous group. The median survival time was similar in patients with histologically confirmed disease (121, 120 and 83 days respectively). Survival times from first treatment and from the date of diagnosis were similar (data not shown).

The estimated effects of the covariates on patient survival from randomization are summarized in *Table 3*. The mortality risk was increased by the presence of distant metastases or a lower Karnofsky score at baseline but not by sex, age (more than 60 years) or previous treatment. Risk ratio estimates for survival from first treatment were similar; however, when survival was measured from the time of diagnosis, previous treatment significantly reduced the mortality risk (risk ratio 0·38 (95 per cent confidence interval 0·22–0·64)).

The median survival time for patients with a good baseline Karnofsky score (90–100 per cent) was 160 days for low-dose intravenous treatment, 150 days for oral treatment and 115 days for high-dose intravenous treatment compared with 67, 62 and 42 days respectively for patients with a Karnofsky score of 80 per cent or less. In patients with histologically confirmed disease, the median survival time was 207 days in the low-dose intravenous treatment group, compared with 149 and 95 days in the oral and high-dose intravenous groups respectively.

The median survival times in patients without metastatic disease were similar in the oral and low-dose intravenous treatment groups (179 and 176 days respectively) and longer than that for patients without metastatic disease who received the high-dose intravenous treatment (135 days). In patients with metastases median survival times ranged from 59 to 65 days.

Clinical progress

Scans of 31 patients thought to have a clinical response were reviewed independently and a partial response or stable

Table 4 Serious adverse events possibly or probably related to treatment

	LiGLA treatment group		
	Oral	Low intravenous	High intravenous
Serious related adverse events			
Body as a whole			
Septicaemia	0	0	1
Swelling	0	0	1
Blood and lymphatic system			
Anaemia	1	0	2
Thrombocytopenia	0	0	1
Cardiovascular system			
Thrombosis	0	0	1
Deep vein thrombosis	0	2	2
Respiratory system			
Pneumonia	1	1	0
Pneumothorax	0	1	1
Other			
Reinsertion of CVP line	0	0	1
Unable to cope with daily travel	0	2	0
Total	2	6	10
Total related adverse events	4	26	64

LiGLA, lithium gamolenate; CVP, central venous pressure

disease was confirmed for nine patients. There was no difference between treatment groups in the development of new clinical manifestations of disease such as anorexia, jaundice and melaena.

Haemolysis

Haemolysis, as detected by haemoglobinuria, was reported as an adverse event in three patients receiving oral treatment and in 26 and 54 patients receiving low- and high-dose intravenous treatment respectively. Mean haemoglobin levels decreased during treatment from 12·1 to 11·2 g/dl in the low-dose intravenous group and from 12·4 to 9·9 g/dl in the high-dose intravenous group, but returned to prestudy levels by the 6-week assessment. Haemoglobin levels did not change during oral treatment. Mean bilirubin concentration rose from 15 to 24 mmol/l in the low-dose intravenous treatment group and from 14 to 30 mmol/l in the high-dose group; these returned to prestudy levels at 6 weeks. There was no change in the oral group. Blood transfusions were given to 15, 12 and 27 patients in the oral, low-dose intravenous and high-dose intravenous groups respectively, during treatment or in the 6 weeks after treatment.

Patients who experienced haemolysis in the low-dose intravenous treatment group (*n* = 26) had a median survival time of 249 days compared with 105 days in patients without haemolysis (*n* = 64). In the high-dose intravenous group the respective survival times were 95 days (*n* = 54) and 81 days (*n* = 41).

Adverse events

There were no significant changes during treatment or during the 6-week post-treatment interval for most of the biochemical criteria. Median serum levels of liver enzymes at week 6 were similar to pretreatment levels. Neither oral nor intravenous treatment had any long-term effect on liver enzymes.

Adverse events were reported by 244 patients (88 per cent). The most frequently reported adverse events, regardless of cause, were nausea, vomiting, abdominal pain and constipation, followed by haemoglobinuria and anorexia. The serious adverse events are summarized in *Table 4*. Six patients were withdrawn from the study as a result of adverse events. Two patients withdrew from oral treatment owing to vomiting and gastrointestinal haemorrhage. Three patients discontinued intravenous treatment because of nausea and vomiting, sepsis or perforated abdominal viscus. One further patient was discontinued from the high-dose intravenous treatment because of an unspecified adverse event.

Twenty-five thromboembolic events occurred in 24 patients, namely deep vein thrombosis in 11 patients, pulmonary embolism in six, deep vein thrombosis and pulmonary embolism in two, axillary vein thrombosis in one and stroke in five patients. Only five of these were considered to be related to the study medication and none was attributed to the method of drug delivery.

Side-effects possibly associated with lithium occurred in 176 patients in this study but were attributed to the study medication by the clinical investigator in only two patients receiving oral treatment, five in the low-dose intravenous group and seven in the high-dose intravenous group. The mean(s.d.) maximum levels of lithium recorded during treatment were 0·40(0·36) mmol/l in the low-dose intravenous treatment group and 0·80(0·48) mmol/l in the high-dose intravenous group. A mean lithium level of 0·15(0·11) mmol/l was recorded for the oral treatment group but this was based on data from only 44 of the 93 patients.

Discussion

This study contains no evidence for a therapeutic effect of systemically administered LiGLA in patients with advanced pancreatic cancer. Survival times in this study for the oral and low-dose intravenous treatment groups were similar to the median survival times of 105 and 130 days reported in the untreated control arms of randomized studies[9,10] and are similar to, or shorter than, survival times obtained in studies using 5-fluorouracil either alone or in combination with other agents. In these other studies, median survival times ranged from 120 to 210 days[11–16].

An earlier study of LiGLA[5] investigated the safety and efficacy of a combined intravenous and oral treatment regimen. The present study was designed to compare survival after two different intravenous dose regimens or oral treatment. No untreated (placebo) group was used because the primary aim was to determine differences between the three treatment protocols. At the time this study began, there was no widely accepted standard treatment for inoperable pancreatic cancer, and this study was conceived as a phase II/III study to look for evidence of a dose-related treatment effect. No beneficial effect of larger doses was observed, and the outcome after oral or low-dose intravenous treatment was similar to that seen in previous studies.

Median survival after high-dose intravenous LiGLA treatment was shorter than after the low-dose intravenous regimen. The reasons for this are not clear. Although more patients in the high-dose group had jaundice at prestudy assessment, all patients had CT and the proportion with distant metastases was similar in all three groups. There were no significant differences between the three groups in the distribution of Karnofsky performance status scores, another factor associated with survival. There are no data on pain or opiate requirement in the three groups. It is known that good pain relief may prolong survival in advanced pancreatic cancer[17], but no data are available on this point, although pain relief and performance status are likely to correlate. It is possible that the difference was due to a tumour-promoting effect of the high-dose intravenous LiGLA, perhaps by an effect on the immune response to the tumour. The shorter survival in the high-dose intravenous group may have been related to the higher proportion of jaundiced patients in that group, perhaps also mediated by effects on the immune system. It is unlikely that the shorter median survival after high-dose intravenous treatment was due to a direct toxic effect of LiGLA, as the early survival curves were similar in the three groups. The survival times of 94–129 days in this study were close to the median survival times (105 and 130 days) seen in the untreated arms of earlier studies[9,10]; it remains possible that the observed difference represents chance variation.

Over half the patients had histological confirmation of the diagnosis of pancreatic adenocarcinoma, and the survival times were similar in patients with or without histological confirmation, suggesting that the results for all patients were reliable.

Haemolysis occurred in a large proportion of patients and was dose related in that it was more common in the high-dose intravenous group. It is likely that haemolysis occurred during rapid intravenous infusion as a result of a direct effect on the plasma membrane of red cells at high plasma concentrations. Haemolysis was less frequent when care was taken to limit the rate of infusion. Features related to haemolysis, such as a rise in bilirubin and a fall in haemoglobin level, were more frequent in the high-dose intravenous group. Patients with haemolysis in the low-dose intravenous group survived longer than those with no haemolysis. Although systemic administration of LiGLA had no effect on the primary tumour, direct tumour injection in an experimental model can slow the growth of tumour nodules[18] and LiGLA is cytotoxic *in vitro*[4]. This raises the possibility that rapid infusion with transient high plasma concentrations of LiGLA sufficient to cause haemolysis might have a direct antitumour effect, perhaps by modifying the implantation or growth of micrometastases.

LiGLA treatment had a favourable toxicity profile. Hair loss, severe nausea and vomiting, blood disorders, fever and skin rashes were not reported. The most frequently reported adverse events were related to the gastrointestinal system and, although these may be attributed to the study medication, they may also be associated with pancreatic cancer. The incidence of serious adverse events considered to be treatment related was very low; the highest incidence was in association with the high-dose intravenous treatment. Thromboembolic disease is a frequent complication in advanced pancreatic cancer with a reported incidence of 7–63 per cent[19,20]. In this study, thromboembolic disorders occurred in 9 per cent of patients.

In this large study of patients with advanced pancreatic cancer, systemic administration of LiGLA led to survival times similar to those seen in historical placebo-treated patients. Although treatment was not toxic, high-dose intravenous LiGLA was associated with a shorter median survival than low-dose intravenous treatment. The encouraging phase II results with LiGLA given orally and intravenously have not been confirmed.

Acknowledgements

The authors thank Simon Kilgour, Graeme Scott and Virginia Watson for assistance in the preparation of this manuscript. Financial support was from Scotia Pharmaceuticals Ltd.

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Prospective randomized multicentre trial comparing stapled with open haemorrhoidectomy

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Background: The aim of this study was to compare the results of conventional open haemorrhoidectomy as currently practised in Italy (group 1) with stapled haemorrhoidectomy using a 33-mm circular stapling device (group 2).

Methods: One hundred patients with symptomatic third- and fourth-degree haemorrhoids were enrolled by five hospitals. Patients were allocated to the two groups according to a centralized randomization scheme featuring five permutated blocks of 20. Preoperative clinical examination and anorectal manometry demonstrated no features of anal incontinence. Patients had a clinical and manometric re-evaluation after operation and were asked to complete a clinical diary. After a median of 16 (range 8–19) months patients were administered a standardized questionnaire by telephone.

Results: Postoperative bleeding requiring haemostatic procedures occurred in three patients in each group. Patients in group 1 complained of moderate pain for a median of 5·3 (range 0–19) days compared with 3·1 (range 0–10) days in group 2 ($P = 0·01$), while severe pain was present for 2·3 (range 0–24) days in group 1 but only for 1 (range 0–14) day in group 2 ($P = 0·03$). The median hospital stay was 2 days in group 1 compared with 1 day in group 2 ($P = 0·01$). In the early days after operation, patients in group 2 had greater difficulty in maintaining normal continence to liquid stools ($P = 0·01$), but after 30 days the continence score was better in group 2 ($P = 0·04$).

Conclusion: Stapled haemorrhoidectomy is as effective as conventional haemorrhoidectomy. Reduced postoperative pain, shorter hospital stay and a trend toward earlier return to work suggest short-term advantages for the stapled technique.

Presented in part at the international meeting Colorectal Disease in the New Millennium, Fort Lauderdale, Florida, USA, February 2000

Paper accepted 11 January 2001

British Journal of Surgery 2001, **88**, 669–674

Introduction

Thomson[1] demonstrated that in patients suffering from haemorrhoids, the specialized 'cushions' of submucosal tissue lining the anal canal slide downwards, together with the anal mucosa, owing to fragmentation of Parks' ligament. It is argued that haemorrhoids are merely the result of this displacement and that prolapse poses an obstacle to venous outflow, resulting in congestion, bleeding and a predisposition towards thrombosis.

Surgical excision of haemorrhoids is effective in treating haemorrhoidal prolapse but is still much feared by patients, above all because of the ensuing postoperative pain. The amount of pain depends on various factors including the subjective pain threshold, the quality and type of anaesthesia, postoperative analgesia and the surgical technique used. Pain is usually worst during the passage of stool owing to direct stimulus of the wound and sphincter spasm. Pain has also been attributed to incarceration of the smooth muscular fibres and mucosa in the transfixed vascular pedicle and to the fact that the anal canal has been bared of its epithelium. Nevertheless, a recent randomized study comparing closed and open haemorrhoidectomy[2] did not reveal significant differences in the linear analogue pain scale and in the need for analgesics between the two methods.

A new approach to the treatment of haemorrhoids has been proposed, a transverse mucosal prolapsectomy at the anorectal junction with a circular stapler. This technique involves interruption of the terminal branches of the superior haemorrhoidal arteries, resection of part of the prolapsed mucosa, lifting the mucosa up in the anal canal, over the high-pressure zone, thus correcting the prolapse and reducing arterial inflow. Preliminary data obtained by Longo[3] are encouraging, featuring reduced postoperative pain, quick recovery and no adverse functional sequelae. In the short term, the circular stapler technique has been reported to be a significantly less painful alternative to Milligan–Morgan haemorrhoidectomy and is associated with an earlier return to normal activity. Because this technique is well accepted by patients and operators, its use has spread rapidly and widely in Europe before the appearance of controlled randomized studies in the medical literature. Two papers that compare stapled haemorrhoidectomy with the Milligan–Morgan procedure have been published recently, both of which report significant advantages for the stapling technique. Mehigan *et al.*[4] reported similar postoperative in-hospital stay but significantly less postoperative pain and an earlier return to work in the group treated with a stapled technique. Rowsell *et al.*[5] also reported significantly less pain after operation, an earlier return to work and a shorter hospital stay among patients treated with stapled haemorrhoidectomy. These two papers did not definitively dispel the scepticism among some coloproctologists[6], however, mainly because of the small number of patients recruited and the short follow-up. Furthermore, functional and manometric evaluation was lacking.

This prospective randomized controlled multicentre study was conducted to compare the effectiveness and safety of stapled haemorrhoidectomy using a circular 33-mm stapler with conventional Milligan–Morgan haemorrhoidectomy[7] in a large cohort of patients.

Patients and methods

One hundred consecutive patients with symptomatic third- and fourth-degree[8] haemorrhoids were enrolled by the five participating hospitals between May 1998 and April 1999. The study was approved by each local ethics committee. After obtaining informed consent, patients of either sex, aged between 25 and 78 years were enrolled. All were candidates for surgical haemorrhoidectomy to treat symptomatic haemorrhoidal prolapse. Patients with concomitant anal disease (fissure, abscess, dermatitis, fistula, Crohn's disease, ulcerative colitis, rectal cancer) and patients on treatment with oral anticoagulants were excluded. Patients were allocated to two groups according to a centralized randomization scheme involving five permutated blocks of 20. Haemorrhoidal prolapse was associated with bleeding in 26 per cent of patients in group 1 and 34 per cent of patients in group 2, with anal pain in 22 and 26 per cent, and with perianal itching in 14 and 6 per cent respectively. Each of the five hospitals received 20 progressively numbered closed envelopes and each operator opened the sealed envelope in the operating theatre before performing the stipulated operation: open haemorrhoidectomy according to Milligan–Morgan (group 1) or prolapsectomy with an Ethicon ILS 33® circular stapler (Ethicon Endo-Surgery, Cincinnati, Ohio, USA) (group 2). Twenty patients were therefore operated by each of the surgeons involved in the trial in their hospital. Patients were prepared for the operation with suppositories or enemas, according to the usual practice in each centre, and the operation was conducted under general or spinal anaesthesia or posterior perineal block.

In open haemorrhoidectomy, the haemorrhoids were prolapsed and retracted from the anal canal, and the subcutaneous submucosal tissue was infiltrated with a solution of adrenaline in saline 1 : 200 000. A V-shaped perianal incision was made at the base of the haemorrhoids, which were dissected from the internal anal sphincter up to the level of the vascular pedicle using diathermy. The pedicle was transfixed as described by Milligan *et al.*[7].

In circular stapled haemorrhoidectomy, one or two purse-string sutures were inserted at least 3 cm proximal to the dentate line using an Eisenhammer or Ferguson retractor. An Ethicon ILS 33® stapler was used to section and staple the mucosal prolapse[9]. All patients were given a high-fibre diet after operation. The use and quantity of analgesics were regulated according to patients' requirements.

The study was divided into two phases: a perioperative and postoperative assessment lasting 5 weeks for each patient (1 week before and 4 weeks after operation), to assess outcome and to check for postoperative complications, and a late assessment of the effectiveness and results of the two techniques in December 1999 after a median postoperative time lapse of 16 (range 8–19) months.

During the week before surgery patients underwent clinical examination, including proctoscopy and anorectal manometry, and were asked to complete a clinical diary that recorded the number of daily evacuations, the presence of blood in the stools, pain during or after evacuation, and the use of analgesics. After operation patients were instructed to take nimesulide (Aulin®; Roche, Milan, Italy) tablets as required. A linear analogue pain scale from 0 to 10 was used to evaluate pain, where 0 corresponded to no pain and 10 to the worst pain imaginable. A postoperative pain score was obtained by adding up the daily pain scores. The results of the linear analogue scale were also subdivided into four groups: absence of pain (0), minor pain (1–3), moderate pain

(4–7) and severe pain (8–10). Any difficulty in evacuation and the level of continence were also recorded in the clinical diary; Wexner's[10] and Williams'[11] scores were used to grade constipation and incontinence.

After the operation, patients were discharged from hospital when free from severe pain that required intramuscular analgesia with ketorolac tromethamine (Toradol®; Recordati, Milan, Italy) regardless of whether evacuation had occurred. Clinical evaluation and anoscopy were repeated 10 and 30 days after surgery, and during follow-up the clinical diary was returned by the patients and evaluated. Time to resumption of normal working activities was recorded. Anorectal manometry was also performed at 30 days. All these data were recorded by the surgeons who performed the operations.

Later follow-up was by telephone interview but patients who complained of residual problems were re-examined clinically by a third surgeon who was not aware of the procedure performed. Persistent symptoms of prolapse, pain, bleeding and patient dissatisfaction denoted failure.

Statistical analysis

Data were analysed using the Mann–Whitney *U* test and the Wilcoxon rank sum test for unpaired data. Manometric data were analysed by Student's *t* test for paired data. The sample size was established before the study. According to Pocock's formula[12], approximately 50 patients in each arm were calculated to be necessary to detect an expected reduction of 40 per cent of the postoperative pain. An α error of 5 per cent and a β error of 20 per cent were considered appropriate.

Results

Characteristics of the patients, type of anaesthesia and immediate postoperative complications are listed in *Table 1*. The two groups were well matched for age, sex and degree of haemorrhoids. There were no significant differences between the two groups with regard to the type of anaesthesia. There were no recorded postoperative local complications but bleeding requiring haemostatic procedures occurred in three patients in each group. After discharge there were no significant differences in the rate of complications.

Postoperative pain

All patients received analgesia in the postoperative period. This consisted of a sufficient number of doses of intramuscular ketorolac tromethamine during hospital stay and of nimesulide tablets after discharge. Patients in group 1 had a mean(s.d.) composite pain score (number of analgesics/number of days of consumption) of 1·5(0·5) compared with 1·4(0·5) in group 2 (*P* not significant). For each patient, a cumulative score was obtained by adding the results of the linear analogue pain scale; the median value was 15 (range 0–82) in group 1 and 11 (range 0–67) in group 2 (*P* = 0·03). Although the mean number of days in which minor pain was experienced was no different in the two groups, there were significant differences as regards moderate or severe pain. Patients in group 1 complained of moderate pain for a median of 5·3 (95 per cent confidence interval (c.i.) 4·2–6·3, range 0–19) days compared with 3·1 (95 per cent c.i. 2·5–3·7, range 0–10) days in group 2 (*P* = 0·01), while severe pain was present for 2·3 (95 per cent c.i. 1·0–3·5, range 0–24) days in group 1 but for only 1 (95 per cent c.i. 0·2–1·5, range 0–14) days in group 2 (*P* = 0·03).

Duration of inpatient stay

Patients were discharged when they no longer required intramuscular analgesics. Postoperative stay was significantly different in the two groups. The median length of hospital stay was 2 (95 per cent c.i. 1·9–2·9, range 0–12) days in group 1 compared with 1 (95 per cent c.i. 1·2–1·5, range 0–3) days in group 2 (*P* = 0·01).

Postoperative functional results

All patients had normal continence before surgery. In the early postoperative period (after 10 days) anal continence was not significantly different in the two

Table 1 Patient features, type of anaesthesia and postoperative complications in the two study groups

	Milligan–Morgan	Stapled
Age (years)*	48(13)	47(14)
Degree†		
Third	36 (72)	35 (70)
Fourth	14 (28)	15 (30)
Incontinence score[11]*	1·00(0)	1·00(0)
Constipation score[10]*	1·03(2·02)	0·50(1·19)
Anaesthesia†		
General	27 (54)	19 (38)
Spinal	16 (32)	18 (36)
Pudendal block	7 (14)	13 (26)
Complications†		
Haemorrhage	3 (6)	3 (6)
Urinary catheter	5 (10)	3 (6)
Difficult evacuation	2 (4)	1 (2)
Bleeding (median days)	6	5

*Values are mean(s.d.); †values in parentheses are percentages. There were no significant differences between groups

groups. Thirty days after operation, incontinence scores were better in the stapled group (P = 0·04). Both groups showed an improvement in constipation score but this was significant only in group 2 (P = 0·02) (*Table 2*).

A total of 33 patients in group 1 and 36 in group 2 underwent both preoperative and postoperative anal manometry. There were no significant functional variations between preoperative and postoperative findings in the two groups (*Table 2*).

Return to working activities

For patients of working age (35 in group 1 and 37 in group 2), the length of absence from work was recorded. Patients in group 1 resumed normal activities after a median of 13 (range 3–25) days and patients in group 2 after 5 (range 1–16) days (P = 0·04).

Long-term evaluation

After a mean period of 16 (range 8–19) months patients were interviewed by telephone and a standardized questionnaire was administered. Rare episodes of prolapse were reported by eight patients in group 2 and frequent episodes by two, whereas only three patients in group 1 reported rare episodes of prolapse in the months following surgery; this difference was statistically significant (P = 0·001). Episodes of bleeding were reported by 16 patients in group 1 and one reported frequent episodes of bleeding while 14 patients in group 2 reported episodes of bleeding (P not significant). Pain was still present occasionally in 14 patients in group 1 and in nine in group 2; one patient in each group reported frequent pain.

Table 2 Functional results and manometric data after operation

	Milligan–Morgan	Stapled
Incontinence (days)*		
Flatus	0 (0–10)	0 (0–11)
Liquid stool	0 (0–5)	0 (0–5)
Solid stool	0 (0–3)	0 (0–6)
Incontinence score[11]†		
Preoperative	1·00(0)	1·00(0)
Postoperative	1·04(0·20)‡	1·00(0)
Constipation score[10]†		
Preoperative	1·03(2·02)	0·50(1·19)
Postoperative	0·27(0·84)	0·14(0·35)§
Maximum resting pressure (mmHg)†		
Preoperative	79(18)	86(14)
Postoperative	78(16)	83(17)
Maximum squeeze pressure (mmHg)†		
Preoperative	146(45)	150(45)
Postoperative	143(47)	154(50)

Values are *median (range) or †mean(s.d.). ‡P = 0·04, §P = 0·02 (Student's t test for paired samples)

Patients who had reported persistence of prolapse at the interview were re-examined clinically. Of the three patients in group 1 who complained of prolapse, one presented only residual external cutaneous fibrous folds, as did six of nine patients in group 2. Therefore, clinically there were no significant differences with respect to the persistence of prolapse between the two groups.

Discussion

The control of pain after haemorrhoidectomy has always been a major concern for surgeons and the main reason for refusing surgery for patients. Multiple complementary treatments have been proposed to reduce postoperative pain, including the use of different surgical instruments (diathermy[13], scalpel, bipolar scissors, laser, ultrasonic forceps), local and/or systemic injection of analgesics[14,15], antibiotics[16], anaesthetics[17,18], or associated procedures such as lateral internal sphincterotomy[19] to reduce postoperative sphincter spasm. All of these treatments have yielded unsatisfactory results because the main unsolved problem is that the sensitive anal mucosa is severely traumatized during the removal of haemorrhoids. The operation proposed by Longo does not damage the anal mucosa, which is lifted higher up in the anal canal by resection of a variable ring of insensitive mucosa at the anorectal junction. It is the redundant mucosa that is resected and not the haemorrhoids when a stapled anopexy is performed.

The aim of this study was not only to compare postoperative pain after the stapled technique with that following the standard operation for haemorrhoids but also to assess the effectiveness of each technique as a definitive cure for haemorrhoids. A comparative evaluation of the results is difficult as the two operations have different aims: stapled haemorrhoidal prolapsectomy removes the prolapse, improves venous drainage and hence congestion of the anal cushions and reduces bleeding, whereas Milligan–Morgan haemorrhoidectomy eliminates the haemorrhoids directly to resolve the symptoms of prolapse and bleeding. Therefore, evaluation of the symptoms seems more useful than a purely anatomical evaluation of the two techniques. The results of this randomized study show that stapled haemorrhoidal prolapsectomy is as effective as the gold standard operation (Milligan–Morgan) in the treatment of third- and fourth-degree haemorrhoids. The number of postoperative complications and relapses was comparable, as was patient satisfaction at 1 year of follow-up.

With regards to postoperative pain, the stapled technique offered a significantly less painful alternative to Milligan–Morgan haemorrhoidectomy. This was particularly evident as regards moderate and severe postoperative anal pain. A direct consequence of this was a significantly shorter hospital stay for the stapled group. The median hospital stay of the Milligan–Morgan group (2 days) is comparable to the 2·5 days reported by Bleday *et al.*[20] and Carapeti *et al.*[21]. Reduced postoperative pain also resulted in an earlier return to working activities for the stapled group. The lack of need for anal medication in patients who had a stapled haemorrhoidectomy may well have favoured this early return to work. Stapled haemorrhoidal prolapsectomy is more expensive than conventional haemorrhoidectomy because of the cost of the device but this may be balanced by a shorter postoperative stay and an earlier return to work.

Analysis of the functional results after haemorrhoidectomy is of particular interest. There was no difference between groups with respect to postoperative faecal continence. However, after 1 month, the Williams' score for incontinence was significantly worse in the Milligan–Morgan group than in the stapled prolapsectomy group. This effect could be related to removal in the Milligan–Morgan operation of a significant part of the sensitive anal mucosa that was spared in the stapler operation. The constipation score was also better after stapled prolapsectomy. This could be due to easier rectal evacuation after removal of the redundant mucosa, as indicated by Pescatori *et al.*[22] in a similar operation for rectal mucosa intussusception.

Finally, there is some difficulty in interpreting the difference between patients' and physicians' views with regard to persistence of the prolapse after operation. Stapled haemorrhoidal prolapsectomy only partially modifies the anal verge in fourth-degree haemorrhoids and whenever bulky cutaneous fibrous folds are present these only regress partially, giving the patient the impression of persistence of the haemorrhoidal prolapse.

The results obtained in this trial suggest that patients with symptomatic haemorrhoidal prolapse derive greater benefit from stapled haemorrhoidal prolapsectomy in the short term and that this operation has at least the same effectiveness as the conventional Milligan–Morgan procedure in the long term. The shorter duration of moderate or severe pain makes stapled haemorrhoidal prolapsectomy well tolerated by patients.

Acknowledgements

The authors thank A. Realis Luc, M. Trompetto, M. Rinaldi, P. L. Sallustio and F. Cortese for their active participation in the study, and Ms M. Pragnell for help in preparing the manuscript.

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Original article

Early gallbladder carcinoma does not warrant radical resection

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Background: This study was designed to address whether gallbladder cancer invading the muscle layer (stage pT_{1b}) is a local disease and whether radical resection is necessary.

Methods: A retrospective analysis of 25 patients with pT_{1b} gallbladder tumours, 13 of whom underwent simple cholecystectomy and 12 radical resection with regional lymph node dissection, was performed. A total of 147 regional lymph nodes was examined for metastasis. The median follow-up time was 95 months.

Results: No patient had blood vessel or perineural invasion on histology. Lymphatic vessel invasion was seen in one patient. Both overt metastasis and micrometastases were absent in all lymph nodes examined. Overall 10-year survival was 87 per cent. The outcome after simple cholecystectomy was comparable to that after radical resection ($P = 0.16$). Two patients who underwent radical resection died from tumour relapse in distant sites.

Conclusion: Most pT_{1b} gallbladder carcinomas spread only locally. Additional radical resection is not necessary when the depth of invasion of gallbladder carcinoma is limited to the muscle layer after simple cholecystectomy.

Presented to the 4th World Congress of the International Hepato-Pancreato-Biliary Association in Brisbane, Australia, May 2000

Paper accepted 23 December 2000

British Journal of Surgery 2001, 88, 675–678

Introduction

The depth of tumour penetration is the most important prognostic factor in patients with gallbladder carcinoma[1–4]. Most mucosal cancers (pathological tumour stage pT_{1a}) and cancers invading the muscle layer (pT_{1b}) spread only locally[5]. Most authors agree that pT_{1a} tumours represent a local disease[1–11]. However, some argue that pT_{1b} tumours may have spread regionally or systemically by the time of presentation[2,4,6,12]. Thus, there is controversy as to whether pT_{1b} gallbladder carcinoma is also a local disease.

Simple cholecystectomy is adequate treatment for patients with pT_{1a} gallbladder tumours, provided that the resection margin is not involved[5]. For pT_{1b} tumours, some authors[1,3,5,7–9] recommend simple cholecystectomy, while others[2,4,6,12] advocate radical cholecystectomy with regional lymph node dissection. The authors reported previously that the outcome after simple cholecystectomy was excellent, regardless of whether regional lymph node dissection was performed, in 11 patients with a pT_{1b} tumour[5]. However, the small number of patients and short follow-up precluded a definitive conclusion.

In this study 25 patients with a pT_{1b} tumour were analysed retrospectively (11 of whom were included in the previous report[5]) with longer follow-up. The aims of this study were to determine whether pT_{1b} gallbladder carcinoma is a local disease and to evaluate the role of radical resection.

Patients and methods

A total of 622 patients with gallbladder carcinoma underwent surgical resection in Niigata University Medical Hospital and its affiliated institutions between October 1981 and July 1999. Some 189 (30·4 per cent) had pT_{1a} tumours and 25 (4·0 per cent) had pT_{1b} tumours. The 25 patients with pT_{1b} disease formed the basis of this study. They included 20 women and five men with ages ranging from 38 to 82 (median 72) years.

Gallbladder carcinoma was suspected or diagnosed before operation by ultrasonography in 11 of the 25 patients; ultrasonographic features included a fungating mass in eight patients and a smooth raised mass in three patients, according to Tsuchiya's classification[13].

Preoperative ultrasonographic diagnosis of the depth of invasion was not possible in any of the 11 patients. In the other 14 patients, the preoperative diagnosis was polypoid lesions of the gallbladder in four and gallstone disease or cholecystitis in ten.

Of the 25 patients, 13 underwent simple cholecystectomy (open in 12, laparoscopic in one) and 12 underwent radical resection. The choice of operation depended on the timing of diagnosis. Radical resection was performed in all of the 11 patients suspected or diagnosed before operation, with the exception of one who was in poor general condition. Simple cholecystectomy was done in patients with presumed benign gallbladder disease. Two patients underwent radical resection as a second procedure following simple cholecystectomy (open in one, laparoscopic in one) for benign disease, once the diagnosis of cancer was established. Of the 12 patients treated by radical resection, four underwent cholecystectomy with regional lymphadenectomy and eight underwent extended cholecystectomy with regional lymphadenectomy, including seven who had wedge resection of the gallbladder bed and one who had wedge resection of the gallbladder bed combined with bile duct resection. Regional lymph node dissection included the lymph nodes in the hepatoduodenal ligament and those posterosuperior to the head of the pancreas[10,11]. No patient had para-aortic lymph node dissection. None died in hospital and adjuvant chemotherapy and/or radiotherapy was not offered. Thereafter, the patients regularly attended outpatient appointments every 3–6 months. Follow-up ranged from 11 to 199 (median 95) months.

The resected specimens were submitted for histological examination. None of the patients had any macroscopic or microscopic evidence of residual tumour. The depth of invasion was determined by examination of multiple sections (range 3–36; median 11 sections) of the whole lesion in each patient and was described according to the tumour node metastasis staging system[14]. The primary tumour was an adenocarcinoma in all patients. Histopathological grade was well differentiated in 20 patients, moderately differentiated in one and poorly differentiated in four patients. A total of 147 regional lymph nodes taken from 18 patients were examined histologically for metastasis (*Table 1*). Two serial sections 3 μm thick, one for routine histological examination and the other for immunohistochemical examination, were cut from each lymph node. Both sections were examined independently. 'Micrometastasis' was defined as a metastasis missed on routine histological examination with haematoxylin and eosin but detected by immunohistochemical evaluation with anticytokeratin antibody, as reported previously[15,16].

Table 1 Clinicopathological characteristics of 25 patients with gallbladder carcinoma invading the muscle layer (stage pT_{1b})

	Simple cholecystectomy ($n = 13$)	Radical resection ($n = 12$)
Age (years)*	74 (65–82)	65 (38–77)
Sex ratio (M : F)	9 : 4	11 : 1
No. of lymph nodes examined*	0 (0–2)	8 (3–32)
No. of positive lymph nodes		
Haematoxylin and eosin	0	0
CAM5·2	0	0
Median survival (months)	95	90

*Values are median (range). CAM5·2, immunohistochemical examination using an anticytokeratin antibody specific for cytokeratins 8 and 18

A mouse monoclonal antibody, CAM5·2 (Becton Dickinson, San Jose, California, USA), which recognizes cytokeratins 8 and 18, was used at a dilution of 1 : 3 for immunohistochemical examination of lymph nodes as described previously[16]. In all 25 patients, both the primary tumour and surrounding non-neoplastic gallbladder epithelium were positive for CAM5·2, with strong intensity in the cytoplasmic membranes.

Statistical analysis

Medical records and survival data were obtained for all 25 patients. The cause of death was determined from medical records. Survival curves were constructed using the Kaplan–Meier method. Death from other causes was treated as a censored case. Differences in survival were evaluated using the log rank test. Statistical evaluation was performed using the SPSS 9·0J software package (SPSS Japan Inc., Tokyo, Japan). $P < 0.05$ indicated statistical significance.

Results

Extent of tumour spread in pT_{1b} disease

Histological examination revealed that no patient had blood vessel invasion. One patient had evidence of lymphatic vessel invasion, but none had perineural invasion. Neither overt metastasis on routine histological examination nor micrometastasis on immunohistochemical examination was identified in any of the regional lymph nodes (*Table 1*). No patient had clinically evident distant metastasis at the time of resection.

Outcome after resection

Five patients died after resection during follow-up. Two patients, who underwent radical resection, died from disseminated tumour 99 and 39 months after resection, without local recurrence. The initial sites of recurrence were the lung and the liver remnant (distant from the gallbladder bed) respectively. The remaining three patients died from other causes including cerebral contusion ($n = 1$), pneumonia ($n = 1$), and primary lung cancer ($n = 1$), with no evidence of recurrent gallbladder cancer. Overall patient survival was excellent, with a cumulative 10-year survival rate of 87 per cent. The outcome after simple cholecystectomy (cumulative 10-year survival rate of 100 per cent) was comparable to that after radical resection (cumulative 10-year survival rate of 75 per cent) ($P = 0{\cdot}16$).

Discussion

In 1976 Nevin *et al.*[1] reported a favourable outcome after simple cholecystectomy for pT_1 gallbladder carcinoma. Since then, many authors[1,3,5,7–9] have considered pT_1 tumour a local disease amenable to cholecystectomy, despite occasional recurrences after resection[4,17–25]. However, two recent patients with pT_{1b} tumours who had late recurrences after resection prompted the current study.

Earlier evidence suggested that both lymphatic vessel invasion and nodal metastasis are rarely found in pT_1 tumours, although pT_{2-4} tumours frequently demonstrate lymphatic spread[2,8,26]. In the previous study of only 11 patients, the authors suggested that most pT_{1b} tumours spread only locally[5]. The present study confirmed this, and also found no nodal micrometastasis in pT_{1b} tumours. These results suggest that pT_{1b} tumour is generally a local disease.

Some authors recommend radical resection with regional lymph node dissection for patients with pT_{1b} disease because of their experience with recurrences after simple cholecystectomy[4,17–20,22,24,25]. However, Tsunoda *et al.*[18] and Hirai *et al.*[21] reported that tumour relapsed even after radical resection in their four patients with pT_{1b} disease. In the present study, two patients died from recurrent gallbladder disease following radical resection. No recurrence was observed in patients undergoing simple cholecystectomy. In addition, the outcome after resection was comparable between patients who did and did not undergo radical resection. Thus, there was no apparent survival benefit in performing radical resection for pT_{1b} disease. Considering the morbidity and mortality rates associated with radical resection[7,10,12], the sporadic patients with tumour relapse reported so far[4,17–25] do not justify the use of radical resection for a pT_{1b} tumour. As shown in this study, preoperative diagnosis of pT_{1b} gallbladder carcinoma is rarely obtained and most pT_{1b} carcinomas are first diagnosed by histopathological examination of a resected specimen. Postoperative diagnosis of pT_{1b} tumour does not warrant additional radical resection.

Acknowledgements

The authors thank Mr Takashi Hatano, Ms Noriko Sekikawa, Ms Motoi Yuda and Ms Mikiko Wakai for technical assistance.

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Short note

Plasma trypsinogen activation peptide in patients with acute pancreatitis

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Paper accepted 21 December 2000

Introduction

Acute pancreatitis (AP) is a common abdominal disorder with a wide clinical spectrum. Twenty per cent of patients develop severe disease with complications. Immediate diagnosis of severe AP is important, since patients benefit from early-phase treatments. In an emergency setting, severity grading is often problematic and there is a need to find more accurate diagnostic methods[1].

Trypsinogen activation resulting in formation of trypsinogen activation peptide (TAP) is thought to be pivotal in the pathogenesis of AP[2]. Raised TAP concentrations in urine accurately distinguish between severe and mild disease[3,4] but, to the authors' knowledge, TAP concentrations in plasma have not been studied previously. The objective of the present study was to determine the role of plasma TAP in AP.

Patients and methods

Between July 1997 and July 1998 a total of 246 patients were enrolled in a prospective multicentre study (Dublin, Helsinki, Liverpool and Ulm)[4]. AP was defined as acute abdominal pain with a typical clinical picture, an increase in serum amylase level to more than three times the upper limit of normal, and typical findings on diagnostic imaging (ultrasonography and/or computed tomography). AP was considered severe if the patient developed local or systemic complications as defined in the Atlanta classification. Exclusion criteria were previous pancreatic surgery, pre-existing chronic pancreatitis, age below 18 years and referral from other hospitals.

Venous ethylenediamine tetra-acetic acid plasma samples were collected within 6 h of admission, every 12 h for 2 days and thereafter at days 3, 4 and 7. TAP levels were measured with a competitive enzyme-linked immunosorbent assay (Biotrin, Dublin, Ireland). Other measurements were done according to hospital routines.

Results

The study population consisted of 74 control patients, 137 patients with mild AP and 35 with severe disease. There were 124 females and 122 males with a median age of 52 years. The aetiology of AP was biliary in 74 patients and alcohol-related in 62 patients; 36 patients had other aetiologies. The median duration of symptoms before admission to hospital was 13 (range 1–153) h.

Levels of TAP in plasma were able to differentiate patients with severe AP from those with mild disease (*Fig. 1*). The difference was statistically significant on admission ($P = 0{\cdot}004$, Mann–Whitney *U* test) and for maximal TAP concentration within 24 h ($P = 0{\cdot}014$), but thereafter TAP values did not have prognostic value. On admission at cut-off 2·8 nmol/l, determined by receiver operating characteristic analysis, plasma TAP had a sensitivity of 70 per cent, specificity of 78 per cent, positive predictive value of 61 per cent and negative predictive value of 84 per cent as a prognostic marker.

The sensitivity and specificity of TAP for differentiation between controls and all patients with AP on admission at an

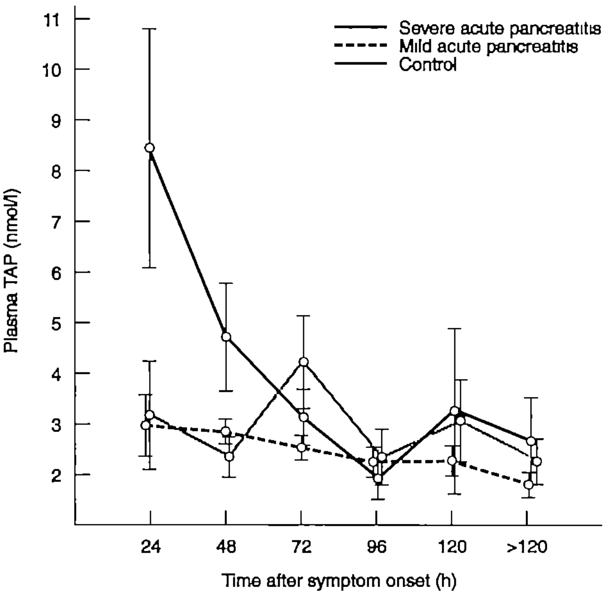

Fig. 1 Time course profile of trypsinogen activation peptide (TAP) in plasma after the onset of symptoms in patients with mild ($n = 137$) and severe ($n = 35$) acute pancreatitis and in controls admitted with the suspicion of acute pancreatitis ($n = 74$). The median delay between onset of symptoms and admission to hospital was 13 (range 1–153) h

optimum cut-off of 1·9 nmol/l were 56 and 64 per cent respectively.

Discussion

The prognostic accuracy of plasma TAP concentration was at a maximum on admission and, using a cut-off of 2·8 nmol/l, the accuracy was comparable or slightly better than that for urinary TAP[4]. However, the prognostic accuracy of plasma TAP declined rapidly after 24 h from admission to hospital.

The plasma concentrations of TAP were generally low, barely exceeding the detection limit of the assay. Urinary TAP concentrations were about 20-fold greater than those in plasma[4]. This can be explained by a short life-time (8 min) of TAP in plasma[5]. The rapid turnover of TAP results in low and fluctuating baseline concentrations in plasma, whereas urinary values reflect a longer time period.

In conclusion, plasma TAP, as measured on admission, correlates well with the severity of AP but the prognostic accuracy declines rapidly thereafter.

Acknowledgements

The authors thank Professor H.-G.Beger (Department of General Surgery, University Hospital of Ulm, Germany), Professor J. Fitzpatrick (Department of Surgery, University College Dublin and Mater Misericordiae Hospital, Ireland) and Dr A. Hietaranta (Clinic of Surgery, Helsinki University Central Hospital, Helsinki, Finland) for their essential contribution to the study. The study was funded by Biotrin, The Rise, Mount Merrion, Dublin, Ireland.

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Short note

Clinicopathological study of hepatocellular carcinoma with diaphragmatic involvement

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Paper accepted 23 December 2000

Introduction

Direct diaphragmatic involvement is found in 10–13 per cent of patients with hepatocellular carcinoma (HCC)[1]. Despite recent advances in preoperative imaging, diaphragmatic involvement by HCC remains an unpredictable intraoperative finding[2]. The pathological features and long-term prognosis of patients with diaphragmatic involvement who undergo operation have not been clarified. Twenty-eight patients with clinical diaphragmatic involvement by HCC underwent *en bloc* resection at the Prince of Wales Hospital in Hong Kong from 1988 to 1999. This study investigated the tumour pathology, evaluated the operative and survival results, and tried to identify prognostic factors, so that the exact role of *en bloc* resection for these tumours could be better defined.

Patients and methods

Liver resection was performed with portal clamping and ultrasonic dissection. Whenever a liver tumour was found grossly adherent to the diaphragm, no attempt was made to dissect the tumour away from the diaphragm. A cuff of the involved diaphragm was removed *en bloc*. The defect was repaired either primarily or with a polytetrafluoroethylene mesh. Pathological features of the specimen, postoperative outcome and patient survival were studied.

Eighteen clinicopathological variables were evaluated for disease-free survival using univariate and multivariate analyses (Cox proportional hazards model): age, sex, hepatitis B status, Pugh–Child grade, total bilirubin level, serum albumin concentration, platelet count, α-fetoprotein level, type of operation, operative blood loss, tumour size, microscopic resection margin, microsatellite tumour nodules, vascular invasion, tumour encapsulation, cellular differentiation, histological cirrhosis and diaphragmatic involvement (adhesion or invasion).

Results

Clinicopathological features are shown in *Table 1*. Histological examination revealed that there was fibrous inflammatory adhesion in 26 of the 28 patients. Only two patients had malignant diaphragmatic muscle infiltration or vascular permeation. During a median follow-up of 21 months, 14 patients had an intrahepatic recurrence. Median disease-free survival was 27 (95 per cent confidence interval (c.i.) 10–45) months and overall survival was 25 (95 per cent c.i. 17–33) months.

Among the 18 clinicopathological factors, a microscopic resection margin of 1 cm was the only significant prognostic factor for poor disease-free survival after *en bloc*

Table 1 Clinicopathological features of 28 patients treated by *en bloc* resection of hepatocellular carcinoma involving the diaphragm

Age (years)*	53 (29–71)
Sex ratio (M : F)	22 : 6
Clinical features	
Hepatitis B surface antigen positive	21
Pugh–Child grading (A : B)	20 : 8
Total bilirubin (μmol/l)*	14·2 (7–46)
Serum albumin (g/l)*	33·5 (19–43)
Platelet count (× 10^9/l)*	227 (120–404)
α-Fetoprotein (ng/ml)*	14 439 (2–184 000)
Type of operation	
Right hepatectomy	16
Extended right hepatectomy	5
Left lateral segmentectomy	1
Resection of one or two segments	3
Non-anatomical resection	3
Operative outcome	
Blood loss (ml)*	1 940 (300–7000)
Morbidity	9
Mortality	1
Pathological features	
Tumour size (cm)*	9·3 (4–17)
Narrow resection margin (< 1 cm)	10
Microsatellite tumour	6
Vascular invasion	10
Encapsulation	20
Cellular differentiation (well : moderate : poor)	4 : 19 : 5
Histological cirrhosis	18
Disease-free survival rate (%)	
1 year	58
2 years	53
3 years	38
5 years	26
Overall survival rate (%)	
1 year	71
2 years	52
3 years	39
5 years	32

*Values are mean (range)

resection (hazard ratio 5·2, $P = 0{\cdot}0087$). The median disease-free survival was 9 (95 per cent c.i. 4–14) months in ten patients with a narrow margin, whereas the 18 patients with an adequate margin (1 cm or more) had longer median disease-free survival of 55 (95 per cent c.i. 4–106) months.

Discussion

En bloc resection is associated with acceptable morbidity and mortality, and may confer long disease-free (26 per cent) and overall (32 per cent) 5-year survival rates. These results compare favourably with recent series of hepatectomy for patients without diaphragmatic involvement[3,4]. This can be explained by the histological finding that diaphragmatic involvement by HCC is mainly due to fibrous adhesion rather than frank tumour invasion. As has been reported previously among patients with HCC and no diaphragmatic involvement[4,5], tumour recurrence was related to a narrow (less than 1 cm) resection margin.

En bloc resection of involved diaphragm is advocated for patients with HCC because it safeguards an adequate resection margin, avoids breaching the tumour capsule and reduces bleeding[2].

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Original article

Revisiting transtibial amputation with the long posterior flap

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Background: The long posterior flap has been the procedure of choice for transtibial amputation for many years, but recently its theoretical basis has been challenged. This study assessed the results with the long posterior flap for leg amputation.

Methods: A prospective cohort study was performed. All patients who were referred to the Dundee Limb Fitting Centre for leg amputation between 1987 and 1996 had details of diagnosis, investigations, procedure, and both operative and functional outcome recorded contemporaneously.

Results: Some 126 patients required a transfemoral amputation and 445 needed a transtibial procedure. Fifty patients having the transtibial operation, who would otherwise have required a transfemoral amputation, had a medially based flap; the remaining 395 patients underwent a transtibial amputation by the long posterior flap technique. Primary healing was achieved in 317 patients, and 11 amputations healed by secondary intention. Fifty-one patients required a local wedge resection and 16 had a secondary transfemoral amputation.

Conclusion: These results compare favourably with those of other published series. The long posterior flap remains to be bettered for routine transtibial amputation.

Paper accepted 7 January 2001

British Journal of Surgery 2001, 88, 683–686

Introduction

Four main reconstructive flaps have been described for transtibial amputation: the skew flap developed in Roehampton[1], the equal sagittal flaps technique as described by Persson[2], the long posterior flap technique as popularized by Burgess and Romano[3], and the medially based flap developed in Dundee[4]. Good results have been reported for all four techniques, but recently the theoretical basis of the long posterior flap has been challenged[5].

At the Dundee Limb Fitting Centre, results with the long posterior flap have been as good as those with any other method. The procedure has stood the test of time and has not been bettered. The present study was a review of results with the operation from 1987 to 1996.

Patients and methods

This was a cohort study of all patients who were referred to the Dundee Limb Fitting Centre for primary leg amputation between 1 January 1987 and 31 December 1996. Data regarding diagnosis, investigations, procedure, and both operative and functional outcome were recorded contemporaneously on a pro forma. During this interval, all patients requiring amputation were referred through the centre.

Patients were selected for transtibial amputation on the basis of Doppler pressure studies, thermography, capillary skin blood flow and clinical examination. A systolic blood pressure of 70 mmHg or greater in the adductor canal was taken as a good prognostic indicator for healing of a transtibial amputation[6], as was a skin temperature higher than 30·4°C at the site of the posterior incision[7] and a capillary skin blood flow greater than 2·5 ml per 100 g tissue per min[8]. Others have used different parameters. Barnes *et al.*[6] used below-knee rather than adductor canal blood pressure. Roon *et al.*[8] considered 2·7 ml per 100 g tissue per min to be an indicator of guaranteed healing, but that transtibial amputation was justified where skin flow was between 2·3 and 2·7 ml per 100 g tissue per min. All patients who needed amputation underwent all the tests; if any result was unfavourable, a transfemoral or medial flap transtibial procedure was performed.

The operations were performed at a specialist infectious diseases hospital and the patient was subsequently transferred to a separate rehabilitation facility.

Operative technique

The anterior skin incision was made one hand's breadth below the tibial tuberosity and deepened through the periosteum and deep fascia without raising any skin flaps. The posterior flap was made long enough to cover the stump comfortably and the longitudinal part of the incision was made to slope slightly posteriorly. The fibula was divided with rib shears 2 cm above the proposed tibial cut, and the tibia was divided with a Gigli saw, chamfering the anterior one third.

The end of the tibia was rasped smooth. The vessels and nerves were ligated as short as possible, and divided. The amputation was completed through the gastrocnemius and soleus muscles without separating them from the skin of the posterior flap. The soleus was excised, as recommended by Gray and Ng[9], and the wound washed with hydrogen peroxide followed by normal saline.

The gastrocnemius was sutured to the anterior periosteum, or to drill-holes in the tibia if this was found to be inadequate, using an absorbable monofilament suture. A suction drain was inserted deep to the muscle and brought out separate from the wound. The deep fascia was closed with a braided absorbable suture and the skin closed with non-absorbable monofilament. A plaster cast was applied over swabs and stump socks with the knee in extension.

The wound was inspected after 5 days and a further plaster cast applied. Mobilization commenced on a temporary prosthesis. A cast was taken for the definitive limb at 21 days and the sutures were removed.

Results

Some 593 patients were referred for leg amputation between 1 January 1987 and 31 December 1996; 126 required a transfemoral procedure and 445 had a transtibial amputation. Twenty-two patients had the amputation at through-knee or through-hip level. Fifty patients, who would otherwise have required a transfemoral amputation, had a medially based flap[4]. Thus, 395 patients underwent a transtibial amputation by the long posterior flap technique. During the study, the overall transtibial : transfemoral amputation ratio was 3·5 : 1. The below-knee : above-knee ratio (including through hip and through knee) was 3 : 1.

Sixty per cent of patients were men and 63 per cent were smokers; the median age was 69 (range 40–90) years. *Table 1* indicates the diagnostic categories. All the patients with peripheral vascular disease and/or diabetes had preoperative angiography. All the diabetic patients also had large vessel peripheral vascular disease.

Primary healing occurred after 317 amputations (80 per cent). In 11 patients (3 per cent) healing was delayed. Local wedge resection was needed to achieve healing after 51 amputations (13 per cent), but 16 (4 per cent) were converted to transfemoral amputation.

Functional outcome was recorded in 379 patients (those who needed transfemoral amputation were excluded). Some 190 patients (50 per cent) used a prosthesis for all activities, 144 (38 per cent) used a prosthesis for short distances but otherwise needed a wheelchair, 25 patients (7 per cent) had a prosthesis fitted but did not walk, and the remaining 20 (5 per cent) had no prosthesis fitted.

Table 1 Reason for transtibial amputation

	No. of patients
Peripheral vascular disease without diabetes	235
Diabetes mellitus	132
Trauma	11
Infection	2
Neoplasm	4
Other	11

Discussion

Studies detailing the outcome for the various techniques of transtibial amputation are listed in *Table 2*. The primary healing rate of 80 per cent in the present study compares favourably with these. In addition, 88 per cent of patients with successful transtibial amputations were fitted with a limb and used it actively; 57 per cent of these patients did not use a wheelchair at all.

The study by Harrison *et al.*[16] of skew *versus* long posterior flap is the only one in which wound healing rate was superior. It is noteworthy that their transtibial : transfemoral ratio was 0·8 : 1, compared with the present rate of 3·5 : 1, making comparison of the results more difficult. In 1972, Robinson[11] published results with a similar transtibial : transfemoral ratio to that in the present study. Termansen's study[13] was a randomized trial of the sagittal and long posterior flap techniques, and was methodologically sound; there was no difference in outcome between the two techniques. It is difficult to put some of the other studies in context as they do not report the number of transfemoral procedures performed during the study interval.

Work by Waters *et al.*[18], and more recently by Pinzur *et al.*[19], has shown that the energy required to walk after a transfemoral amputation is much greater than that following a transtibial amputation. In the elderly patient this can make the difference between walking or being non-ambulatory. It is important to balance this against the higher rate of primary healing when transfemoral amputation is chosen in marginal circumstances.

Table 2 Summary of published results of amputation

Reference	Year	Long posterior flap	Sagittal	Skew	Diabetic (%)	Vascular (%)	Other (%)	Transtibial : transfemoral ratio	Primary healing (%)	Secondary healing (%)	Wedge excision (%)	Conversion to transfemoral (%)
Hunter-Craig *et al.*[10]	1970	15			13	73	14		53	20	17	20
Robinson[11]	1972	54			30	68		3·6 : 1	76		11	13
Barnes *et al.*[6]	1976	53						1·5 : 1	38	13		17
Mooney *et al.*[12]	1976	190							91	4	2	3
Termansen[13]	1977	47			39	57	4	1·4 : 1	38	21	9	15‡
			41						41	17	2	24§
Roon *et al.*[8]	1977	113			49	45	17		69	17		10
Alter *et al.*[14]	1978		17						71	24	6	
		14							¶			
Yamanaka and Kwong[15]	1985		23						74	4	13	9
Harrison *et al.*[16]	1987	71						0·8 : 1	89*			11
				38				0·8 : 1	95*			5
Falstie-Jensen *et al.*[17]	1989	84			54	46			69	18	13†	
			56		45	55			82	2	16†	
Present study	2000	395			33	59	7	3·5 : 1	80	3	13	4

*Percentages for both primary and secondary healing. †Percentages for wedge excision and conversion to transfemoral amputation. ‡Seventeen per cent and §15 per cent died before healing or were not healed at follow-up. ¶Figures do not add up to total

The technical difficulty of a procedure is an important consideration when extrapolating the results of papers to the population as a whole. The long posterior flap is technically easier than the other techniques for those learning the operation.

The use of the medial flap allows some patients to have a transtibial amputation even if they do not have sufficient viable tissue for a long posterior flap. It is, however, more technically demanding and the long posterior flap should remain the routine procedure of choice.

It bears acknowledgement that the operative procedure does not stand in isolation and that the present results are as much a function of selection criteria and the rehabilitation programme as of operative technique.

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Original article

In-hospital mortality from abdominal aortic surgery in Great Britain and Ireland: Vascular Anaesthesia Society audit

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Background: The mortality rate associated with elective aortic aneurysm repair is widely assumed to be in the region of 5 per cent. This figure does not take into consideration the effect of pre-existing risk factors. The Vascular Anaesthesia Society of Great Britain and Ireland conducted a large audit to estimate the in-hospital mortality rate associated with non-emergency infrarenal aortic surgery throughout the British Isles, and to determine the influence of risk factors on mortality rate.
Methods: This was a multicentre, prospective audit of 177 hospitals throughout the UK and Ireland. Data were collected by questionnaire to include all patients undergoing elective or urgent surgery for infrarenal abdominal aortic aneurysm or aortoiliac occlusive disease over 4 months.
Results: Nine hundred and thirty-three patients were recruited into the audit. The overall mortality rate was 7·3 per cent. Factors increasing the risk of death by up to fivefold included age over 74 years, urgent surgery, operation for occlusive disease, limited exercise capacity, a history of severe angina or cardiac failure, the presence of ventricular ectopics and abnormalities suggesting ischaemic heart disease on electrocardiography.
Conclusion: Although the in-hospital mortality rate was similar to previously published figures, the rate increased considerably when commonly encountered risk factors were present.

Some early data from the audit were presented at the annual meeting of the Vascular Anaesthesia Society, Exeter, UK, September 1999

Paper accepted 30 January 2001

British Journal of Surgery 2001, 88, 687–692

Introduction

The perioperative care of high-risk surgical patients is a topical subject[1,2]. These patients have high morbidity and mortality rates and consume a relatively large proportion of health service resources[3–5]. Patients requiring surgery on the abdominal aorta are at high risk.

Published studies looking at mortality and factors predictive of an adverse outcome following abdominal aortic surgery have often been retrospective or performed over a prolonged interval, which may make their findings less applicable to present practice. Few of the studies have examined the population in the British Isles.

The studies suggest a mortality rate for elective infrarenal aortic surgery of between 4 and 7 per cent[6–14], which may not have changed in 20 years[8]. Factors associated with an increased mortality rate include increasing age[8,11,15], chronic renal impairment[13,15,16], hypertension[13] and surgery in centres that perform few aortic operations[7,14].

In an attempt to obtain current information on the mortality rate among patients undergoing elective infrarenal abdominal aortic surgery in the British Isles, the audit committee of the Vascular Anaesthesia Society of Great Britain and Ireland undertook a multicentre study from February to May 1999 inclusive.

Patients and methods

A pilot audit was undertaken in early 1998. All members of the Vascular Anaesthesia Society were invited to participate. In addition, for the main audit, consultant anaesthetists in all hospitals identified as conducting vascular surgery were contacted. Replies expressing willingness to participate were received from individuals in 177 hospitals, throughout Great Britain and Ireland.

Data collection

The audit was designed to generate as many replies as possible without overburdening the individual contributors, who were participating voluntarily. All open infrarenal abdominal aortic aneurysm (AAA) repairs, and infrarenal aortoiliac or aortofemoral grafts for aortic occlusive disease (AOD) were included. Elective and urgent operations were included, urgent being defined as an operation that needed doing on the next available operating list. Emergency operations were excluded. Indication for operation or degree of urgency was not sought. The audit was conducted from February to May 1999 inclusive. Data were collected by questionnaire. Questions were divided into those concerning the hospital type, size and facilities, the patient's age, sex and preoperative co-morbidity, the type of anaesthetic and surgery, and the outcome.

Confidentiality

The voluntary reporting of sensitive outcome data could be compromised unless absolute anonymity was assured. Consequently data were stored in such a way that patients treated in the same centre were labelled as such, but that individual centres were unidentifiable.

Conduct

Invitations to participate in the audit were sent to the identified 177 potential contributing hospitals. Data collection forms (questionnaires) and instructions were sent in mid-January 1999, and four reminders were sent at intervals during the audit. Participants were telephoned to encourage a high response rate.

Analysis

The effect of various factors on the probability of death was investigated using logistic regression. Initial analyses included the participating hospital as a random effect (fitted in MLWin (Institute of Education, London, UK)) but the variance component associated with this factor was always negligible, so the analyses reported below are conventional logistic regressions fitted in GLIM (NAG Ltd., Oxford, UK)[17].

Most of the factors fitted are categorical. It was considered unwise to assume a linear effect for age, so this variable was divided into the categories 65 or less, 66–74 and 75 or more years. The number of operations performed in a centre was taken as a measure of the volume of cases, which may reflect varying degrees of surgical and anaesthetic experience, and which may in turn be reflected in the mortality rate. Centres were classified as being low volume if two or fewer operations were carried out each month and as high volume if more than four operations were carried out each month. The remaining centres were classified as being of medium volume.

Results

Of the 177 volunteering hospitals, nine subsequently withdrew. Data were received from 118 hospitals, seven of which performed no aortic surgery during the audit, giving a return rate of 70·2 per cent. A total of 933 satisfactorily completed individual questionnaires were returned including 777 for patients who had AAA repair and 156 who had aortic replacement for AOD. The overall mortality rate for all patients in the audit was 7·3 per cent (68 of 933 patients). In both groups the majority of patients had an elective procedure (*Table 1*).

Cause of death was reported for 63 of the 68 patients who died. The death was labelled as 'cardiac' in 23 patients, 12 of whom died within 3 days of surgery. Multiorgan failure was implicated in 27 deaths, all but four of which were more than 4 days after surgery. Respiratory failure was the sole cause of six deaths, and surgical factors were blamed for four deaths. Cause of death in the remaining three patients was subarachnoid haemorrhage, pulmonary embolism and gastrointestinal bleed.

Overall, 189 (20·3 per cent) of the patients were women. This proportion was 17·2 per cent for patients having surgery for AAA and 35·3 per cent for patients having surgery for AOD. The ratio of men to women in the elective and urgent groups was similar (*Table 2*).

Age was not recorded for three patients who were excluded from further analysis. The age range of the remaining patients was 39–90 years. Patients who had surgery for AOD were younger than those who had surgery for AAA (*Table 2*).

Table 1 Deaths following aortic surgery according to urgency of operation

	Elective	Urgent	Total
Aneurysm	42 of 671 (6·3)	13 of 106 (12·3)	55 of 777 (7·1)
Occlusive disease	10 of 143 (7·0)	3 of 13 (23·0)	13 of 156 (8·3)
Total	52 of 814 (6·4)	16 of 119 (13·4)	68 of 933 (7·3)

Values in parentheses are percentages

Table 2 Number and age of patients according to sex, indication for operation and degree of urgency

	Men		Women		Total	
	n*	Age (years)†	n*	Age (years)†	n	Age (years)†
All patients	744 (79·7)	70 (39–90)	189 (20·3)	71 (42–86)	933	71
Aneurysm	643 (82·8)	71 (39–90)	134 (17·2)	74 (42–86)	777	72
Occlusive disease	101 (64·7)	60 (39–79)	55 (35·3)	60 (45–77)	156	60
Elective	651 (80·0)	70 (39–88)	163 (20·0)	71 (45–86)	814	70
Urgent	93 (78·2)	70 (39–90)	26 (21·8)	74 (42–85)	119	72

*Values in parentheses are percentages; †values are median (range)

Table 3 Volume of aortic surgery related to mortality rate

	Low volume				Medium volume				High volume			
	Elective		Urgent		Elective		Urgent		Elective		Urgent	
	n	Mortality (%)	n	Mortality (%)	n	Mortality (%)	n	Mortality (%)	n	Mortality (%)	n	Mortality (%)
Age (years)												
< 65	74	3	11	18	86	5	16	6	34	3	4	0
65–75	127	7·1	15	7	146	6·8	20	5	102	2·9	15	0
⩾ 75	79	10	15	27	111	7·2	20	25	52	13	3	67

Volume classification: low, ⩽ 2 operations per month; medium, 2–4 operations per month; high, > 4 operations per month

Risk factors for death

The initial analysis considered the effect of age, whether the operation was urgent or elective, and the volume of operations performed in each centre (*Table 3*). Analysis by logistic regression confirmed that the mortality rate was higher in the older age group ($\chi^2 = 13{\cdot}06$, 2 d.f., $P = 0{\cdot}001$), and that urgent operations carried greater risk ($\chi^2 = 6{\cdot}28$, 1 d.f., $P = 0{\cdot}012$). There was no evidence that the number of operations performed by each centre influenced outcome. High-volume centres did not have a higher prevalence of risk factors than low-volume centres (*Table 4*). Fitting the sex of the patient, after allowing for age and urgency, showed a marginally increased risk for women (*Table 5*). Fitting the type of operation, either occlusive disease or aneurysm repair, again after allowing for age and urgency, showed that AOD had a higher risk ($\chi^2 = 4{\cdot}45$, 1 d.f., $P = 0{\cdot}035$).

In all the following analyses the effects were reported after accounting for age, urgency and operation type.

Effect of cardiac health and related medication

The effect of previous myocardial infarction was negligible ($\chi^2 = 0{\cdot}07$, 1 d.f., $P = 0{\cdot}75$). Individually, severe angina, history of left ventricular (LV) failure and use of diuretics were significant factors that increased the risk of operation (*Table 6*). These three factors were closely interlinked in the sense that if any one was in the model, the effect of the others was reduced.

Assessment of LV function by echocardiography was obtained in 437 of the 933 patients. The mortality rate of the patients who had echocardiography was 8·2 per cent compared with 6·5 per cent for those who did not: adjusted odds ratio (OR) 1·31 (95 per cent confidence interval (c.i.) 0·79–2·18) ($P = 0{\cdot}29$). Patients who had an echocardiogram were grouped into three categories according to LV function: good, impaired and severely impaired. There was no significant difference in mortality rate between the three groups, although the number in the severely impaired group was small.

Electrocardiographic (ECG) appearance indicative of ischaemic heart disease (IHD), the presence of ventricular ectopics (VE) and the existence of any rhythm other than sinus were investigated. Individually both IHD and VE were associated with increased risk (*Table 6*). When IHD was in the model VE remained a significant factor ($\chi^2 = 4{\cdot}40$, 1 d.f., $P = 0{\cdot}036$). There was evidence that these variables were acting independently; each was associated with higher risk even in the presence of the other variable: after adjusting for VE, the OR for IHD was 1·71 (95 per cent c.i. 1·02–2·88) and, after adjusting for IHD, the OR for VE was 2·44 (95 per cent c.i. 1·12–5·34).

Table 4 Prevalence of risk factors in centres grouped according to volume of operations reported

	Percentage of patients with risk factor		
	Low volume	Medium volume	High volume
Aortic occlusive disease	17	19	14
Urgent operation	13	14	11
Age > 74 years	29	33	26
Exercise capacity < 50 yards	11	13	10
IHD on ECG	38	48	47
VE on ECG	5	6	7
Severe angina (NYHA IV)	4	4	3
Taking diuretics	25	29	22
History of heart failure	13	13	8

ECG, electrocardiography; IHD, ischaemic heart disease; VE, ventricular ectopics; NYHA, New York Heart Association classification

Table 5 Numbers of patients, mortality rate, odds ratios and significance for general data, after taking account of the three other factors in the table

	n	Mortality (%)	Odds ratio	*P*
Age (years)				
< 65	225	4·4	–	
65–74	425	5·7	1·31 (0·62–2·79)	
> 74	280	12·1	3·00 (1·46–6·29)	0·001
Sex				
Men	742	6·5	–	
Women	188	10·6	1·63 (0·94–2·84)	0·094
Urgency				
Elective	811	6·4	–	
Urgent	119	13·5	2·38 (1·24–4·14)	0·012
Operation				
Aneurysm	774	7·1	–	
Occlusive disease	156	8·3	2·28 (1·10–4·75)	0·035

Values in parentheses are 95 per cent confidence intervals

Table 6 Cardiac risk factors, after taking account of age, urgency and operation type

	n	Mortality (%)	Odds ratio	*P*
Angina (NYHA)				
< III	743	6·9	–	0·13
III	154	7·0	1·01 (0·51–2·02)	
IV	33	18	2·83 (1·07–7·42)	
ECG evidence				
IHD				
No	517	5·2	–	
Yes	413	9·9	1·88 (1·13–3·13)	0·015
VE				
No	875	6·6	–	
Yes	55	18	2·89 (1·34–6·20)	0·012
Sinus rhythm				
Yes	839	7·3	–	
No	91	8	0·88 (0·38–2·04)	0·78
History of heart failure				
No	819	5·6	–	
Yes	111	12·8	2·10 (1·12–3·93)	0·03
On diuretics				
No	689	5·0	–	
Yes	241	10·4	2·01 (1·20–3·38)	0·01
LV function*				
Good	301	7·3	–	0·21
Impaired	124	9·7	1·33 (0·63–2·80)	
Severely impaired	12	17	2·86 (0·56–14·60)	
Exercise capacity				
> 1 mile	291	3·0	–	
500 yards–1 mile	187	5·3	1·48 (0·58–3·77)	
50–500 yards	156	11·5	3·13 (1·34–7·30)	
< 50 yards	23	17	5·02 (1·34–18·8)	

Values in parentheses are 95 per cent confidence intervals. *Determined by echocardiography. NYHA, New York Heart Association classification; ECG, electrocardiographic; IHD, ischaemic heart disease; VE, ventricular ectopics; LV, left ventricular. *P* values for angina and echocardiography are tests for trend

Effect of exercise capacity

Exercise capacity was assessed as the ability to walk more than 1500 metres, 500–1500 metres, 50–500 metres or less than 50 metres, as reported by the patient. This analysis omitted 33 patients with no information on exercise capacity and 243 patients with claudication. There was a clear effect of exercise capacity: χ^2 (linear trend) = 10·15, 1 d.f., P = 0·006; χ^2 (non-linear effect) = 0·22, 2 d.f., P = 0·90 (*Table 6*).

Effect of serum creatinine

This analysis was performed on 902 patients, as baseline creatinine was not recorded in 28. Creatinine was skewed and was therefore logged before analysis. Raised preoperative serum creatinine level was associated with an increased mortality rate. However, when age was included in the model, this association disappeared. Forty patients required renal support after operation. The geometric mean of the serum creatinine level in these patients was 121 mmol/l compared with 102 mmol/l in the 862 patients who did not require renal support (ratio of geometric means 1·19 (95 per cent c.i. 1·08–1·31); P = 0·0002). Allowing for age, the adjusted geometric mean for baseline creatinine in those requiring support was unchanged at 121 mmol/l, compared with 102 mmol/l in those who did not need support (ratio of geometric means 1·19 (95 per cent c.i. 1·09–1·30)). Requirement for renal support increased the mortality rate from 5·9 to 35 per cent (χ^2 = 48·35, 1 d.f., P < 0·00001).

Discussion

This study reports data on 933 patients who had general anaesthesia for open aortic surgery. Endovascular stent procedures were excluded because these patients are too highly selected for meaningful comparisons to be made with open repair.

The primary outcome measured was in-hospital mortality rate. This is more relevant than the 30-day mortality rate, as some patients with a protracted postoperative course may die as a consequence of major surgery after 30 days, and would not be counted in conventional studies in which 30-day mortality rate is the outcome. In addition, in-hospital data are easier to collect and therefore more likely to be accurate.

It is not possible to be sure that data were received on all patients who had surgery in the audit interval, from each contributing hospital; it is possible that the data were selective. However, as the measures taken to ensure confidentiality were extensive, and widely known before the audit began, this is unlikely. If any participants did send selective data, however, it is likely that the true mortality rate was worse. Mortality rates from each individual centre were not calculated; these would be highly variable because the number of patients submitted by each centre was small (mean fewer than eight).

The overall mortality rate following non-emergency aortic surgery was 7·3 per cent. When urgent operations were excluded, the mortality rate was 6·4 per cent. The mortality rate associated with elective AAA repair based on reported series ranges from 4 to 7 per cent. This is in keeping with the present findings, and it may be concluded that the mortality rate for open AAA repair in the UK and Ireland is acceptable when taken as a whole, although there may be considerable variation between centres. It is clear that individual risk factors may affect the risk of death markedly.

The present data suggest that several factors are associated with an increased mortality rate. For example, urgent operations conferred 2·38 times the risk of death and patients aged over 74 years had 3·00 times the risk of death compared with patients under 65 years. There was a wide variation in mortality rate associated with urgent operations between centres with different workloads (*Table 3*), but the numbers were too small for this to be significant. Surgery for occlusive disease carried a risk 2·28 times that for aneurysm disease, after correcting for other factors. The mortality rate from operation for AOD was 8·3 per cent, yet the median age of the patients was 12 years less than that of patients who had AAA repair. Aortic operations for AOD are high risk and perhaps other forms of treatment should be considered.

Surgical centres that performed a low volume of operations had results as good as those with a higher workload. This may be accounted for by low-volume centres referring higher risk patients to high-volume centres, although there was no evidence for this in the study (*Table 4*).

An association between cardiac health indices and death was suggested. Severe angina, a history of LV failure, ECG evidence of IHD or VE were all associated with a significantly increased mortality rate after aortic surgery. It is likely that the increased mortality rate seen in patients taking diuretics was due to the association with heart failure or hypertension, rather than an effect of the diuretics themselves. Previous myocardial infarction has not been found to be a risk factor. These findings broadly agree with existing cardiac risk indices[18,19], with the exception of the importance of previous myocardial infarction and moderate angina. Newer methods of managing high-risk cardiac patients, such as β-blockade, epidural analgesia and improved monitoring, may have overcome the increased risks.

The apparent association between serum creatinine concentration and death was in fact due to a combination of the effect of age and its effect on serum creatinine level. However, patients who required postoperative renal support had a 20 per cent higher preoperative serum creatinine level, and these patients had a mortality rate of 35 per cent.

One of the principle aims of the audit was to determine the risk of death from aortic surgery when various risk factors are taken into consideration. This will add to the information available when considering aortic surgery for each patient. Study of the ORs presented in *Tables 5* and *6* allows a simple appreciation of operative risk for an individual. Advice given to the patient may therefore be more accurate, and consent may be better informed.

The second aim was to produce national data against which individual vascular surgical units can compare themselves. This has become even more pressing in recent months with the requirements of clinical governance.

Acknowledgements

The authors thank the anaesthetists around the British Isles who contributed to the audit, the Committee of the Vascular Anaesthesia Society of Great Britain and Ireland for commissioning and supporting the audit, Ms Deborah Beaton for managing the database, and the staff of the Audit Department, Freeman Hospital, Newcastle upon Tyne, for invaluable assistance in organizing the mailings. Funding was provided by the Vascular Anaesthesia Society of Great Britain and Ireland. Further help with the costs of mailing was provided by the Audit Department, Freeman Hospital.

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Original article

Prospective study of primary anastomosis following sigmoid resection for suspected acute complicated diverticular disease

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Background: A primary anastomosis after resection of the sigmoid colon for suspected acute complicated diverticular disease has the advantage of saving the patient a secondary operation for restoring bowel continuity. Fear of anastomotic leakage often deters surgeons from making a primary anastomosis.

Methods: A series of 45 patients who underwent primary anastomosis was studied prospectively to evaluate the feasibility of a primary anastomosis following acute sigmoid resection. Acute Physiology And Chronic Health Evaluation (APACHE) II score, Mannheim Peritonitis Index (MPI) and Hughes' peritonitis classification were used to classify patients and to detect factors predictive of postoperative outcome. Death, anastomotic leakage and septic complications were main outcome measures.

Results: Neither anastomotic leakage (four of 45 patients) nor death (three of 45) was related to a higher MPI, APACHE II or Hughes' score. More postoperative septic complications were seen in patients with a MPI over 16. Death, anastomotic leakage, reintervention and wound infection were observed more frequently in patients who presented with colonic obstruction than in those with abscess or perforation.

Conclusion: Primary anastomosis is safe and effective in non-obstructed cases of complicated diverticular disease. Colonic obstruction seems to be a risk factor for the development of postoperative complications.

Paper accepted 21 December 2000

British Journal of Surgery 2001, 88, 693–697

Introduction

Two-stage resection and subsequent anastomosis is widely practised in the management of complicated diverticular disease[1,2]. The diseased segment of bowel is resected and an end-colostomy fashioned with oversewing of the distal colonic or rectal stump (Hartmann's procedure). This technique is supposed to reduce septic complications related to anastomotic leakage and intra-abdominal sepsis. However, Hartmann's procedure has serious disadvantages, particularly the presence of a stoma and subsequent and often demanding reintervention for restoration of colonic continuity. Restoration of bowel continuity is not completed in 25–70 per cent of patients who are therefore left with a permanent stoma[3–7]. These disadvantages have encouraged resection with primary anastomosis as an alternative option[4,5,8–11].

To determine whether resection with primary anastomosis without temporary faecal diversion is safe enough to warrant broader application in a randomized clinical trial, patients who presented with acute complicated diverticular disease were treated with resection and primary anastomosis and studied prospectively.

Patients and methods

From 1995 to 1997, 45 consecutive patients, treated for acute complicated diverticular disease in five large teaching hospitals in the Netherlands, were studied prospectively. The criterion for inclusion was a perioperative diagnosis of

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The Editors have satisfied themselves that all authors have contributed significantly to this publication

acute complicated diverticular disease. Exclusion criteria were previous irradiation of the pelvic organs and faecal incontinence.

Acute complicated diverticular disease was defined as perforated diverticulitis with paracolic abscess, localized pelvic peritonitis or diffuse peritonitis, or colonic obstruction due to recurrent episodes of diverticulitis with stenosis. All patients were treated with acute resection of the sigmoid colon and primary anastomosis, without a stoma. The anastomosis was described as handsewn or stapled, one or two layer, and as end to end, end to side or side to side. The type of anastomosis was based on personal preference. Intraoperative additional faecal spill, oedema or induration of both colonic resection edges was recorded. The resected sigmoid colon was sent for histological examination.

General anaesthesia was usually provided. Operations were carried out by consultant grade staff specialized in gastrointestinal surgery, assisted by or assisting a senior resident. Patients were admitted routinely for observation to the 24-h recovery department after operation, with selective admission to the intensive care unit. Nasogastric tube feeding was employed on indication.

Classification of disease

Several classifications were used for accurate staging and identification of risk factors predictive of postoperative morbidity and death. The Acute Physiology And Chronic Health Evaluation (APACHE II) score[8,12,13] was determined. At operation the severity of abdominal sepsis was quantified on the basis of the Mannheim Peritonitis Index (MPI)[14–17]. The MPI takes into account variables such as age, sex, organ failure, malignant neoplasm, duration of peritonitis, extent of spread within the peritoneum and characteristics of the peritoneal fluid. The severity and extent of peritoneal inflammation was assessed according to the modified Hughes' classification[4,18]: grade I, phlegmonous diverticulitis or peridiverticulitis; grade II, perforated diverticulitis with localized pelvic peritonitis or paracolic abscess; and grade III, perforated diverticulitis with diffuse faecal or purulent peritonitis.

Description of postoperative outcome

Postoperative complications were divided into three categories: (1) procedure-related complications, i.e. anastomotic leakage[19] or wound infection; (2) disease-related complications, i.e. sepsis, the systemic response to infection as defined by Bone *et al.*[20,21], bacterial peritonitis (pus or bowel content in the peritoneal cavity)[14] and intra-abdominal abscess formation (local collection of pus); and (3) general complications, i.e. myocardial infarction, atelectasis and pneumonia. Reinterventions were recorded, with a description of the indication for reintervention and the type of procedure performed. Mortality was defined as in-hospital death, irrespective of the interval between primary operation and death.

Analysis

Patients were divided into different categories with respect to APACHE II score (0–5; 6–10; 11 or more points) and MPI (16 or less; more than 16). MPI subdivision was based on a median MPI score in the study population of 16 points. Patients with colonic obstruction were separated from the group with other types of complicated diverticular disease, i.e. perforation, abscess formation or peritonitis. The two groups were compared for postoperative complications and mortality rate.

To test for differences between the two groups χ^2 and t tests were used as appropriate. Differences were considered significant at $P < 0{\cdot}05$.

Results

Forty-five patients with an intraoperative diagnosis of acute complicated (peri)diverticulitis (eight with obstruction; 37 with abscess or perforation) were included in the study. There were 24 men and 21 women of mean age 67 (median 71, range 37–97) years. Medical history revealed pulmonary disease in 11, cardiovascular disease (ischaemic heart diease or hypertension) in 17, rheumatic disease in three, diabetes mellitus in two and use of corticosteroids in two patients.

The mean APACHE II score for all patients was 8 (median 7, range 1–20). The mean intraoperative MPI score was 18 (median 16, range 6–37). According to Hughes' peritonitis classification 14 patients had grade I, 21 had grade II and ten patients had grade III peritonitis, four of whom had diffuse faecal peritonitis. Forty-one patients had diverticular disease on histological examination. At histological examination a carcinoma was found in the resected sigmoid colon in five patients, one of whom also had diverticular disease. These patients were not excluded.

Intraoperative faecal spill was reported in five patients. Oedema or induration of the colonic resection edges was observed in nine patients. In 40 patients the anastomosis was handsewn (one layer in 25 patients, two layers in 15), and in five patients a stapled anastomosis was performed. The anastomosis was end to end in 29 patients, end to side in nine and side to side in seven patients.

Postoperative outcome

The overall mortality rate was 7 per cent (three of 45 patients). The cause of death was abdominal sepsis in the presence of anastomotic leakage in all three patients. Anastomotic leakage was seen in four patients, one of whom survived. Disease-related complications were frequent: sepsis in 23 of 45 patients, bacterial peritonitis in four and intra-abdominal abscess formation in two. Myocardial infarction occurred in two patients and respiratory complications (atelectasis and pneumonia) in nine patients. Reintervention was necessary in eight patients. In four patients reintervention was necessary for anastomotic leakage. In these cases, the anastomosis was dismantled and an end-colostomy was constructed. In two patients a planned second-look operation was performed. In one patient an abscess was drained under ultrasonographic guidance and in the other reintervention was necessary to reconstruct the abdominal wall because of wound rupture.

Table 1 Acute Physiology And Chronic Health Evaluation II score and postoperative outcome

	APACHE II score		
	0–5 (*n*=14)	6–10 (*n*=20)	≥11 (*n*=11)
Death	0	1	2
Anastomotic leakage	0	1	3
Reintervention	2	2	4
Wound infection	2	2	0
Intra-abdominal abscess	0	1	1
Bacterial peritonitis	1	1	2
Sepsis	4*	10	9
Myocardial infarction	0	0	2
Pneumonia	3	3	3

APACHE, Acute Physiology And Chronic Health Evaluation. *$P < 0\cdot05$ *versus* APACHE II ≥ 11 (χ^2 test)

Table 2 Acute Physiology And Chronic Health Evaluation II scores and postoperative outcome in relation to Mannheim Peritonitis Index

	MPI ≤ 16 (*n*=24)	MPI > 16 (*n*=21)
APACHE II score*	6 (1– 12)†	10 (1–12)
Peritonitis grade		
I	10	4
II	13	8
III	1‡	9
Death	1	2
Anastomotic leakage	1	3
Reintervention	4	4
Wound infection	3	1
Intra-abdominal abscess	0	2
Bacterial peritonitis	0‡	4
Sepsis	8‡	15
Myocardial infarction	0	2
Pneumonia	5	4

*Values are median (range). APACHE, Acute Physiology And Chronic Health Evaluation; MPI, Mannheim Peritonitis Index. †$P < 0\cdot05$ *versus* MPI > 16 (Mann–Whitney test); ‡$P < 0\cdot05$ *versus* MPI > 16 (χ^2 test)

Evaluation of different patient categories

In *Table 1* postoperative outcome is described for three categories of patients with different APACHE II scores. Death, anastomotic leakage or reintervention, as main outcome variables, were equally divided over the different APACHE II categories. Sepsis was reported more frequently in patients with an APACHE II score of 11 or more than in the group with a score of 0–5 ($P < 0\cdot05$, χ^2 test).

Table 2 shows APACHE II scores and outcome in relation to different MPI categories. The APACHE II score for patients with a MPI score of 16 or less was significantly lower than that for patients with a higher MPI score ($P < 0\cdot05$, Mann–Whitney test). Significantly more patients with grade III peritonitis were observed in the group with a MPI over 16 ($P < 0\cdot05$, χ^2 test). Postoperative bacterial peritonitis and sepsis were both significantly more frequent in patients with a MPI over 16 ($P < 0\cdot05$, χ^2 test). There was no relation between the incidence of death, anastomotic leakage or reintervention and the MPI score.

Table 3 Comparison of patients with colonic obstruction and others with complicated diverticular disease

	Colonic obstruction (*n*=8)	Abscess/perforation (*n*=37)
APACHE II*	9·1(4·0)	7·8(4·3)
MPI*	17·2(8·6)	18·1(7·1)
Peritonitis grade		
I	7†	7
II	0†	21
III	1	9
Death	3†	0
Anastomotic leakage	3†	1
Reintervention	4†	4
Wound infection	3†	1
Intra-abdominal abscess	1	1
Bacterial peritonitis	2	2
Sepsis	3	20
Histological carcinoma	3†	2
Myocardial infarction	1	1
Pneumonia	3	6

*Values are mean(s.d.). APACHE, Acute Physiology And Chronic Health Evaluation; MPI, Mannheim Peritonitis Index. †$P < 0\cdot05$ *versus* abscess/perforation (χ^2 test)

Anastomotic leakage was seen in four patients. Three of the four patients with anastomotic leakage were operated for colonic obstruction due to diverticular disease (of whom one also had carcinoma of the sigmoid colon). Oedema of the colonic resection edges was seen in these patients. Three patients died after acute reintervention for dismantling the anastomosis and construction of an end-colostomy. Although age, APACHE II score and MPI were similar in patients with obstruction the postoperative outcome was worse in these patients than in those with other types of complicated diverticular disease (*Table 3*).

Discussion

Complicated diverticulitis can present as phlegmonous peridiverticulitis, localized peritonitis, fistulation or obstruction. If the perforation is not locally contained, free perforation with generalized faecal or purulent peritonitis can ensue. At some stage within this spectrum there is clinical deterioration with an insufficient response to conservative treatment and urgent surgical intervention is required. There is still considerable debate concerning the optimum timing of restoration of bowel continuity; whether this is done during the acute procedure or is delayed until after complete recovery. In the literature there are few prospective studies of the surgical management of complicated diverticular disease and the results are not uniform[22,23]. Most studies are based on retrospective analyses[5,10,11,24–31]. In theory a primary anastomosis is to be preferred, because it saves hospital readmission and relaparotomy for secondary anastomosis. The current study was a prospective analysis of resection and primary anastomosis, based on the hypothesis that the morbidity and mortality rates associated with complicated diverticular disease are primarily determined by the state of the disease and that a large bowel anastomosis has the same healing capacity in an otherwise healthy patient in the presence of peritonitis.

In the present cohort of patients the decision to operate was based on clinical deterioration and suspected (localized) perforation with peritonitis. All except two patients had a MPI below 29, suggesting local peritonitis in the left lower quadrant. Regardless of the state of intraperitoneal contamination, sigmoid colon resection was performed to remove the septic focus and to treat the underlying disease. The observed mortality rate of 7 per cent compares favourably with that reported in the literature for acute complicated diverticular disease (10–30 per cent)[5,23,24]. The anastomotic leak rate reported in this study is comparable to the rate reported in literature for patients with peritonitis and obstruction due to complicated diverticular disease or distal colorectal tumour, which varies from 5 per cent[31] to 20 per cent[24], and does not exceed the rate of leakage (10 per cent) reported in secondary elective reconstruction after Hartmann's procedure[30]. The incidence of anastomotic leakage in this study was not related to a higher APACHE II, MPI or Hughes' peritonitis classification. This indicates that the severity of the disease was not the main determinant of anastomotic complications.

An important observation in this study is that only one patient developed anastomotic leakage without fatal outcome in the subgroup of 37 patients with complicated diverticular disease without obstruction. Of the eight patients who presented with colonic obstruction (suspected to be due to diverticular disease), three patients developed anastomotic leakage and subsequently died. In colonic obstruction the proximal bowel end can be oedematous and this condition is theoretically more prone to cause anastomotic complications. From larger studies it can be concluded that a primary anastomosis is often feasible in the obstructed colon[23,24]. Since in this study the subgroup of patients who presented with colonic obstruction was small, there may be a type II error.

In conclusion, this study in 45 consecutive patients showed that a primary anastomosis without decompression after sigmoid resection for complicated diverticular disease without obstruction did not lead to a higher anastomosis-related complication rate than that reported in the literature after elective reconstruction of Hartmann's procedure. Only colonic obstruction seems to be an additional risk factor for the development of complications. Whether Hartmann's procedure would have prevented the fatal outcome in these patients remains uncertain. A randomized trial, comparing Hartmann's procedure with primary anastomosis without protection, may clarify how best to treat different subgroups of patients with varying degrees of peritonitis in acute complicated diverticular disease.

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Original article

Endoscopic axillary surgery in breast cancer

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Background: The aim was to provide an assessment of the current status of endoscopic axillary surgery in patients with breast cancer.

Methods: Fifty-three patients underwent endoscopic lymphadenectomy. The surgical efficiency (operating time, number of resected nodes, intraoperative and postoperative complications), short-term morbidity (duration of drainage, total lymph flow, seroma rate) and long-term outcome (pain, numbness, mobility, strength, oedema) were assessed. The incidence and severity of different arm symptoms were compared with the results of 396 patients treated with a conventional axillary procedure. Finally, all available data relating to endoscopic axillary surgery were reviewed.

Results: The operating time ranged from 60 to 150 min. A mean 17 (range 10–28) lymph nodes was resected. The extent of postoperative lymphorrhoea (mean 372 ml) and the seroma rate (eight of 34 patients) were not significantly reduced in comparison with conventional surgery. The assessment of long-term morbidity revealed fewer disturbances of sensitivity and a decreased rate of severe symptom intensity for pain, oedema and complaints related to mobility.

Conclusion: Despite excellent visualization of anatomical landmarks and improved long-term morbidity, endoscopic lymph node dissection cannot be regarded as a suitable technique for routine axillary management in breast cancer because of long operating times.

Paper accepted 1 January 2001

British Journal of Surgery 2001, 88, 698–703

Introduction

The therapeutic benefit associated with conventional surgery for the assessment of axillary node status is not significant[1,2] and patients often experience serious postoperative morbidity[3,4]. The need for new surgical staging techniques has been discussed widely in the literature. Lymphatic mapping – the identification of node-negative patients by resection of a single (or a few) representative lymph node(s) – is one new alternative. Conversely, the endoscopic approach for axillary lymphadenectomy is based on minimally invasive access and allows the resection of lymph nodes under microsurgical conditions. The aim of both procedures is to ensure local tumour control and to maintain the amount of information yielded by the axillary status, while at the same time decreasing surgery-related morbidity.

Suzanne *et al.*[5] first published the details of an endoscopic approach for axillary lymph node dissection in breast cancer; others confirmed the feasibility of the technique[6–9]. Validation of a new surgical procedure, however, requires objective evaluation of the method's oncological efficiency, long-term outcome and cost-effectiveness in comparison with standard techniques. In the present study endoscopic axillary lymph node dissection was analysed in a series of 53 patients. The long-term outcome of these patients was compared with the results of a large series of 396 patients who had undergone conventional operation.

Patients and methods

Between October 1997 and September 1999, 53 endoscopic axillary lymph node dissections were performed following lipoaspiration of axillary fat. Only patients with a small tumour (less than 3 cm on palpation) and clinically negative axillary node status were included in the study. One patient with suspicious axillary lymph nodes requested an endoscopic approach, as she suffered from metastatic disease and had exhibited significant restriction of arm function following previous axillary surgery on the contralateral side.

All operations were performed by the same surgeon (T.K.), experienced in both breast surgery (more than 500 conventional axillary dissections) and endoscopic pelvic operations (more than 1500 procedures). During an initial

Table 1 Criteria for the assessment of subjective symptoms

	Degree of intensity (score points)				
Symptom	0	1	2	3	4
Pain	No pain	Following intense physical activity	Following daily chores	Permanent	Impaired sleep
Strength (restriction)	None	Mild	Moderate	Fairly severe	Severe
Mobility (restriction)	None	Mild	Moderate	Fairly severe	Severe
Oedema	None	Following intense physical activity	Following daily chores	Permanent, little impairment	Permanent, severe impairment

learning phase of 15 operations, endoscopic lymphadenectomy was routinely supplemented by a small incision in order to verify the effectiveness of the procedure. Thereafter, complete endoscopic resection of axillary lymph nodes was performed. Operating time, intraoperative and postoperative complications, lymph node harvest, lymphorrhoea and seroma formation were recorded. Operating time was analysed retrospectively from the anaesthesia report. After completion of primary treatment (surgery, radiation, chemotherapy), and following an interval of at least 6 months, all patients were invited for a follow-up examination in order to document the long-term outcome.

Morbidity was assessed by means of a self-report by questionnaire (five-point scale) and clinical examination. The degree of symptom intensity for pain, oedema, arm strength and mobility was evaluated. Arm sensation was tested clinically. The criteria for the assessment of subjective and objective symptoms are presented in *Tables 1* and 2.

The outcome of endoscopically treated patients was compared with that of 396 women who had conventional lymphadenectomy. These patients had been examined earlier by the same team of examiners (one physiotherapist, one sports therapist) according to the same protocol[10]. In that study, neither the type of surgery (lumpectomy *versus* mastectomy), nor the time interval between surgery and follow-up (at least 6 months), nor other factors such as patient age, the number of resected nodes (at least ten), the number of invaded nodes, the level of dissection (level I–II *versus* level I–III), adjuvant treatment or surgeon had any influence on any of the symptoms examined in this series; hence the data should be comparable with the results for endoscopically treated patients. There was no apparent preselection.

Diagnosis was made either by preoperative core-needle biopsy or by excision biopsy with intraoperative frozen-section examination. Axilloscopy was performed beginning with aspiration of axillary fat. The liposuction technique and the endoscopic procedure have been described elsewhere in detail[11]. Postoperative management was identical for both endoscopic surgery and conventional axillary lymph node dissection. A suction drain was inserted routinely and remained in place for at least 4 days. Early shoulder motion began the day after operation with gentle arm movements under the guidance of a physiotherapist. Postoperative lymphorrhoea was recorded daily.

Resected lymph nodes (for both procedures) were examined following a standardized protocol by the same team of pathologists. Axillary fat was filtered from the formalin solution, embedded in paraffin and examined thoroughly for muscle fibres, fragments of lymph nodes and tumour cells. All specimens were subjected to conventional haematoxylin and eosin staining.

All data were entered into a database developed with the INGRES® database system (Computer Associates International, Islandia, New York, USA). Data control was achieved by comparing the printouts of each patient with the source data. The incidence of different arm symptoms was compared with Fisher's exact test (two sided). $P < 0{\cdot}05$ was considered statistically significant.

Table 2 Criteria for clinical evaluation (objective morbidity)

	Degree of intensity (score points)				
Symptom	0	1	2	3	4
Strength (isoton) (°)*	0–20	21–40	41–60	61–80	> 80
Mobility (°)†	≤ 10	11–25	26–40	41–55	> 55
Oedema (%)‡	≤ 10	11–20	21–30	31–40	> 40
Numbness	No				Yes

*Difference in angle of abduction reached by outstretched arm with a weight of 3 kg between operated and contralateral arm. †Range of motion for abduction; difference between operated and contralateral arm. ‡Difference in arm volume between operated and contralateral arm: $V = \Sigma U_i^2/\pi = U_1^2 + U_2^2 \ldots + U_n^2/\pi$

All patients who had endoscopic surgery gave written informed consent. The study was approved by the local ethics committee.

Results

Clinical and disease characteristics of the 53 patients with endoscopic axillary dissection and 396 women with conventional surgery are summarized in *Table 3*.

After a learning phase of 15 patients in whom the effectiveness of the endoscopic operation was controlled through a small incision, complete endoscopic axillary lymph node dissection was achieved in 38 patients. In almost every case, excellent exposure of anatomical landmarks was achieved. Four operations had to be converted into open procedures because of intraoperative difficulties, including gas leakage (one), extensive lymph node involvement (one) and severe obesity (two). Within the learning phase two patients developed subcutaneous emphysema. In both operations gas leakage was noted and the gas flow was augmented (greater than 1 l/min). Following a strict limitation of gas flow (less than 1 l/min) and intra-axillary pressure (7–9 mmHg), no further subcutaneous emphysema was observed. Intraoperative blood loss was minimal and no bleeding complication occurred either in the learning phase or later. In one patient with a pT_{mic} tumour, complete removal of lymph nodes was not performed because the endoscopically resected blue-stained sentinel node was negative. Of the remaining 31 patients with complete endoscopic axillary dissection, a mean of 17 (median 17, range 10–28) lymph nodes was removed. In contrast, the mean number of removed nodes was 21 (median 21, range 5–48) in a series of 396 conventional axillary dissections. The difference in lymph node harvest was statistically significant ($P < 0\cdot006$).

Table 3 Details of patients undergoing axillary surgery

	Endoscopic ($n = 53$)	Conventional ($n = 396$)
Age (years)*	50 (24–85)	55 (22–86)
Time since operation (months)*	16 (7–21)	32 (6–96)
Tumour stage†		
T_1	37 (70)	243 (61)
T_2	15 (28)	130 (33)
T_3	0 (0)	10 (3)
T_4	1 (2)	13 (3)
Type of operation		
Breast conserving	53	306
Mastectomy	—	90
No. of removed nodes*	17 (10–28)	21 (5–48)
Axillary status		
Negative	39	242
Positive	14	154

*Values are median (range); †values in parentheses are percentages

Signs of tissue trauma following lipoaspiration were encountered in 35 (66 per cent) of the 53 patients. Fragments of lymph nodes were found in 22 (42 per cent), muscle fibres in 27 (51 per cent) and tumour cells in one (2 per cent) of the 53 patients. The finding of tumour cells in the aspirated fat was made in the patient who had undergone endoscopic surgery at her own request and who did not fulfil the stated inclusion criteria of clinically negative axillary node status. Final histological examination revealed complete node invasion with perinodal infiltration of the axillary fat in this patient.

The mean duration of axillary lymph drainage was 6 (range 4–11) days. The mean drain volume was 372 (range 30–1345) ml. Operating time ranged from 60 to 150 (mean 110) min. Even with the experience of more than 30 patients, the length of operation could not be

Table 4 Published results of endoscopic axillary dissection

	Present study	Salvat *et al.*[12]	Suzanne *et al.*[13]	Brun *et al.*[14]	Harder *et al.*[8]	Kamprath *et al.*[9]	Cangiotti *et al.*[7]
Year	2001	1996	1997	1997	1998	1999	1999
No. of patients	53	20	72	26	50	33	15
Technique	LS + ER + (I)	LS + ER	LS + ER	LS + ER + I	LS + ER	BD + ER	LS + ER
No. of removed nodes*	17 (10–28)	13 (5–21)	14 (0–32)	13 (1–15)	13 (5–25)	14 (2–28)	16 (10–24)
Total drain volume (ml)*	372 (30–1345)	—	65	275	—	40 ml/day	580 (240–1880)
Duration of drainage (days)*	6 (4–11)	—	No drainage	5	—	4 (1–7)	6 (4–12)
Seroma (%)	24	25	3	—	16	9	7
Other postop. complication	1 abscess	—	—	—	—	1 abscess	—
Operating time (min)	60–150†	—	—	61(11)‡	—	30–130†	—
Local recurrence	—	2	—	—	—	—	—
Length of follow-up (months)	7–21	—	18	1–12	4–24	—	—

*Values are mean (range); †range; ‡mean(s.e.m.). LS, liposuction; ER, endoscopic resection; I, incision; BD, blunt dissection reduced reliably to less than 90 min. Conventional axillary surgery is scheduled for 30–45 min in this department.

After operation eight of 34 patients developed a seroma requiring aspiration. In three, temporary fever in excess of 38°C occurred, but disappeared after aspiration and antibiotic treatment. One abscess had to be drained surgically.

The data from 53 endoscopic axillary lymph node dissections, as well as the results of 216 cases published to date in six other series, are shown in *Table 4*.

Thirty-five patients were re-examined for long-term morbidity at least 6 months after operation. All of these patients completed primary treatment (surgery, adjuvant chemotherapy, radiotherapy). Twenty-one patients had undergone complete endoscopic surgery and 14 received an additional incision either to check the endoscopic result or for technical problems. There was no measurable difference between patients who had undergone endoscopic lymph node dissection and those in whom the operation was supplemented by a small incision (learning phase) with regard to any of the subjective and objective symptoms studied.

When patients treated endoscopically were compared with those who had a conventional operation, significantly more patients in the conventional group reported numbness (289 (73 per cent) of 396 *versus* six of 21; $P < 0·05$). The proportion of patients who felt free of any discomfort relating to the subjective and objective symptom strength, mobility, oedema or pain was almost identical in the two groups (*Table 5*).

With regard to the incidence of fairly severe or severe symptoms, there was a definite advantage for patients who had endoscopic surgery. For all subjectively assessed symptoms, as well as for all clinically evaluated symptoms, fewer patients with severe impairment were recorded in the endoscopic group (*Table 5*).

Discussion

In a series of 53 endoscopic axillary lymph node dissections the experience of others was confirmed, that the endoscopic

Table 5 Long-term morbidity following conventional and endoscopic axillary lymphadenectomy

	Conventional technique (*n* = 396)	Liposuction + endoscopy only (*n* = 21)	Liposuction + endoscopy + incision (*n* = 14)	Total liposuction + endoscopy (*n* = 35)
Subjective symptoms				
Strength				
No restriction	102	7	3	10
Fairly severe or severe	72	2	1	3
Mobility				
No restriction	118	4	5	9
Fairly severe or severe	56	0	0	0
Oedema				
No swelling	177	10	7	17
Permanent	85	1	0	1
Pain				
No pain	107	5	5	10
Permanent or impaired sleep	91	1	0	1
Objective symptoms				
Numbness	289	6	4	10
Strength				
No restriction	224	15	10	25
> 40°	15	1	0	1
Mobility				
No restriction	216	13	9	22
Mean restriction (°)	21	13	8	11
> 55°	57	1	0	1
Oedema				
Severe	36	0	0	0
None	306	18	14	32
Mean difference in volume		3·3	2·4	2·9
Subjective and objective symptoms				
No symptoms	12	1	2	3

approach for axillary surgery is feasible and allows excellent identification of anatomical landmarks in most patients. The magnifying effect of the endoscope facilitates precise performance of all surgical steps. The results of the present study, as well as data from other series, demonstrate that endoscopy may satisfy the oncological demand for both safe tumour control and adequate staging[5–9,12,13]. Technical problems and intraoperative complications were rare. Reviewing 269 endoscopic axillary dissections reported in the literature, severe haemorrhage or motor nerve injury was rarely observed[9,12]. Insufficient anatomical orientation in obese patients may be a technical problem, as is tissue removal, especially when large pieces are resected. The use of a removal bag is feasible but technically challenging, and leads to an enlargement of the incision.

Suzanne *et al.*[13] described a daily postoperative lymph flow of only 23·4 ml, leading them to renounce wound drainage. In the present series, however, an overall mean drain volume of 372 ml was observed, leading to 5–6 days of drainage. Other groups have reported similar results, and most surgeons would not omit axillary drainage after endoscopic surgery[6,7,9]. The drain volume of conventional procedures is reported to be 322–447 (range 23–1100) ml[15,16]. Suzanne *et al.*[13] described seromas in only 2·8 per cent of their patients, whereas eight (24 per cent) of 34 patients in the present study needed aspiration of a postoperative seroma. Others have reported seroma rates of 6·6–25 per cent for the endoscopic technique[7,8,12]. Following conventional axillary surgery seromas are reported in 2–59 per cent[15,17–19]. There is no clear advantage of the endoscopic approach over conventional surgery in terms of reducing postoperative lymphorrhoea.

Whether the endoscopic approach is associated with a higher rate of tissue traumatization (capsular lesions, cell ruptures) is controversially discussed in the literature[12,14,20]. Damage to soft tissue was observed in 66 per cent of the present patients (histologically proven muscle fibres or fragments of lymph nodes in the aspirated fat). Liposuction is not an atraumatic technique. Some authors fear tumour cell spillage and trocar-site metastases, as has been observed in the endoscopic surgery of other cancers[21]. Others argue that the implantation of metastases is dependent on tumour biology rather than mechanical spread[22,23]. Two local recurrences have so far been reported following endoscopic axillary surgery; in both, extensive axillary involvement had been observed[13].

Most authors report excellent functional results following endoscopic axillary surgery[7–9,13]. None, however, has performed an accurate assessment of shoulder–arm morbidity that allows a comparison with the outcome after conventional surgery. Shoulder–arm morbidity is difficult to assess, because numerous symptoms must be evaluated. Furthermore, the clinical evaluation does not necessarily correspond to the subjective self-assessment[10]. There were significantly fewer sensation problems in patients who had endoscopic dissection in the present study than in the group of women who had conventional surgery. For all other symptoms there was only a slight improvement in the overall incidence of various subjective complaints and objective measurements. However, a significant reduction of severe symptom intensity was observed for almost all symptoms examined. Although a definitive comparison between the two techniques requires a prospective randomized trial, these data suggest that the endoscopic approach may reduce the overall morbidity of axillary lymph node dissection.

The main critical issue in endoscopic surgery was the prolonged operating time, which could not be reduced to a reasonable length even after considerable experience. Endoscopic lymphadenectomy would be difficult to implement in a daily clinical routine. Endoscopic axillary dissection cannot yet be recommended as a standard procedure for staging the axilla in breast cancer. Because of the uncertain oncological risk associated with the liposuction procedure, the endoscopic approach is restricted to small, probably node-negative, cancers. For these patients, however, sentinel node biopsy represents an attractive alternative[24,25].

Acknowledgements

The authors thank Gisela Büchele (Department of Biometrics and Medical Documentation, University of Ulm) for support in the collection and analysis of data. They also thank Annette Rebstock for word processing, and Dr Richard A. Mason for revision of the English text.

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Original article

Sentinel node biopsy with technetium-99m colloidal rhenium sulphide in patients with breast cancer

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Background: Sentinel node biopsy is emerging as a technique to replace routine axillary lymph node dissection. The lymphatic mapping technique is still at a developmental stage and no standard technique exists. This study used technetium-99m colloidal rhenium sulphide with a mean particle size of 100 (range 50–200) nm for sentinel node mapping.

Methods: Eighty-seven patients with breast cancer, but no clinical evidence of axillary metastasis, were studied. One day before operation technetium-99m colloidal rhenium sulphide was injected at four points into breast tissue surrounding the tumour. Lymphoscintigraphy was performed 2 h after injection, and surgery was usually performed after 20 h. A hand-held γ probe guided sentinel node biopsy.

Results: Lymphoscintigraphy revealed axillary hot spots in all patients. During operation, the sentinel node was identified in all 87 patients (100 per cent). The number of sentinel nodes per patient ranged from 1 to 5 (mean 2). Metastatic sentinel nodes were identified in 37 of 87 patients. There were no false negatives.

Conclusion: This study suggests that technetium-99m rhenium sulphide is a suitable agent for sentinel node mapping in patients with breast cancer.

Paper accepted 8 January 2001

British Journal of Surgery 2001, **88**, 704–707

Introduction

The sentinel node is defined as the first lymph node in a regional lymphatic basin which receives lymph flow from a primary tumour[1,2]. The sentinel node is thought to be the first lymph node encountered by tumour cells metastasizing through lymphatic channels. In theory, if the sentinel node contains no metastatic cancer, the remainder of the nodal basin will also be free from metastases. Therefore, nodal dissection can be avoided in patients with a negative sentinel node.

In 1992, Morton *et al.*[3] reported a dye technique for lymphatic mapping and sentinel node biopsy in clinically node-negative patients with melanoma. In the field of breast cancer, sentinel node biopsy was reported by Krag *et al.*[4] in 1993 and by Giuliano *et al.*[5] in 1994 using a radiopharmaceutical agent and isosulfan blue dye respectively. In 1996, Albertini *et al.*[2] reported a combined procedure using both these agents. Since these reports, many investigators have published their results with lymphatic mapping and sentinel node biopsy for breast cancer[6–13], with promising results. However, the lymphatic mapping technique remains in a developmental stage and no standard technique exists today.

When lymphatic mapping is performed with a radiolabelled colloid, the choice of radiocolloid is vital because distribution depends greatly on particle size. The ideal radiocolloid particle size is reported to be between 10 and 100 nm[1], or 10 and 200 nm[14].

This paper reports results of sentinel node biopsy in patients with breast cancer using technetium-99m colloidal rhenium sulphide (NANOCIS®, CIS bio-international, Gif sur Yvette, France) with a mean particle size of 100 (range 50–200) nm[14].

Patients and methods

Eighty-seven consecutive patients with breast cancer but no clinical evidence of axillary metastasis were enrolled between February 1999 and June 2000. Informed consent was obtained and the project approved by an institutional review board at Fukushima Medical University. Patient characteristics are summarized in *Table 1*. The mean age of

Table 1 Characteristics of 87 patients undergoing sentinel node biopsy for breast cancer

Mean (range) age (years)	51 (28–79)
Preoperative diagnosis*	
Excision biopsy	7 (8)
Fine-needle or core biopsy	80 (92)
Mean (range) tumour size (cm)	2·7 (0–7·4)
Tumour stage*	
T_1	33 (38)
T_2	46 (53)
T_3	8 (9)
Multiple tumours*	
Single	80 (92)
Multiple†	7 (8)
Operation*	
Modified radical mastectomy	44 (51)
Breast-conserving operation	43 (49)

*Values in parentheses are percentages. †Six patients had two tumours; one patient had three tumours

patients was 51 (range 28–79) years, and the mean primary tumour size was 2·7 cm.

One day before operation 0·3–0·4 ml (37–185 MBq) technetium-99m colloidal rhenium sulphide was injected at four points (3, 6, 9 and 12 o'clock positions) into breast tissue surrounding the tumour (or biopsy cavity). In some patients radiocolloid was also injected into breast tissue surrounding a second, or multiple, tumours. In the first 40 patients lymphoscintigraphy was performed 2, 4 and 19 h after injection. In other patients lymphoscintigraphy was performed 2 h after injection. Anterior and anterior-oblique projections of the breast and axilla were obtained. Usually, the operation was performed the next day, 20 h after radiocolloid injection. Guided by a hand-held γ probe (neo 2000^{TM}, Neoprobe Corporation, Dublin, OH, USA), sentinel node biopsy was performed before partial or total mastectomy and complete axillary dissection. Internal mammary node dissection was not performed. After removal of the hottest node in the axilla, additional nodes were sought in the remainder of the nodal basin. In general, sentinel node biopsy continued until the axilla remainder counts decreased to less than 10 per cent of hottest node activity.

The sentinel node was sent for frozen-section examination; it was cut into 2-mm slices. Remaining frozen tissue was thawed, fixed and embedded, to produce permanent sections. Standard histological examination was performed subsequently. In 65 patients sentinel nodes were stained for cytokeratin. Non-sentinel nodes were evaluated by routine haematoxylin and eosin staining.

Results

Lymphoscintigraphy revealed axillary hot spots in all 87 patients. Ipsilateral internal mammary nodes were visualized in nine patients. The hot spot was seen on the 2-h scan and remained identifiable through the 19-h scan (*Fig. 1*). During operation, sentinel nodes were identified in all 87 patients (sentinel node identification rate 100 per cent). The number of sentinel nodes ranged from 1 to 5 (mean 2).

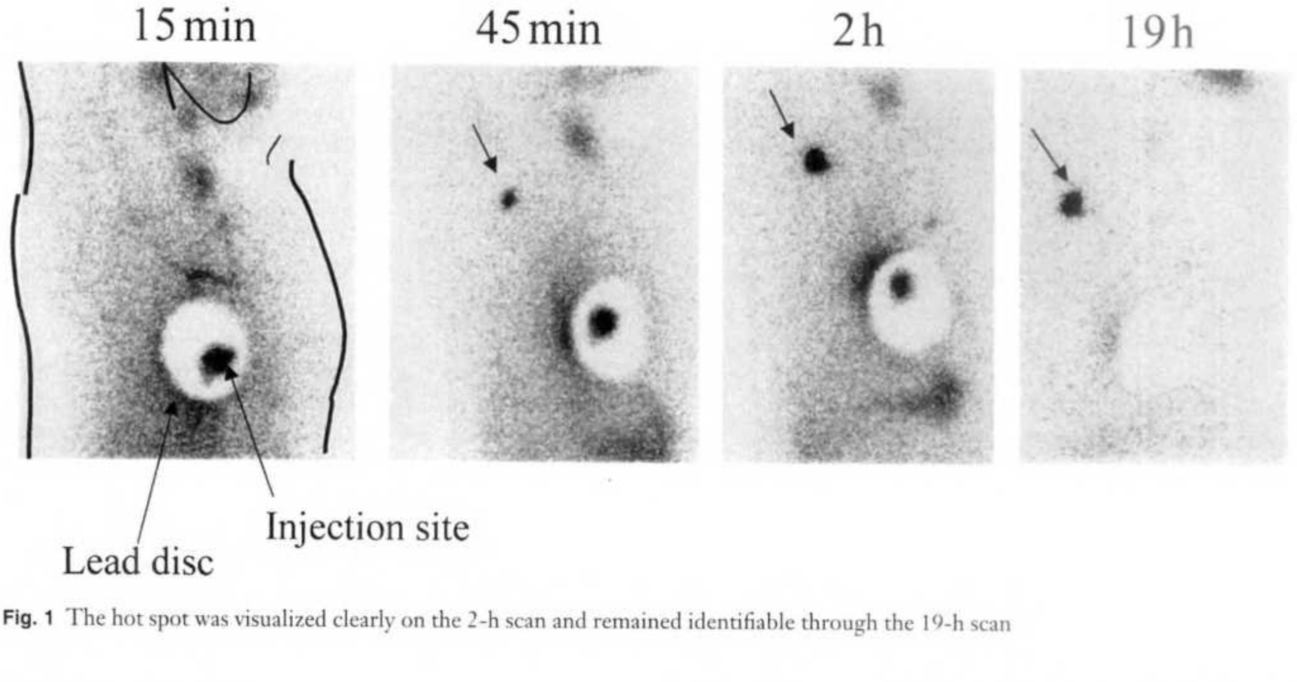

Fig. 1 The hot spot was visualized clearly on the 2-h scan and remained identifiable through the 19-h scan

Primary tumour size did not affect the mean number of sentinel nodes (T_1, 2; T_2, 2; T_3, 2). Radioactivity of sentinel node ranged from 20 to 2943 counts per second (c.p.s.) and the mean radioactivity of 182 sentinel nodes was 480 c.p.s. The mean number of non-sentinel nodes in each axilla was 18.

In 37 of the 87 patients, the sentinel node was positive. No false negatives (sentinel node negative and non-sentinel node involved) occurred. In three of seven patients with multiple tumours, and in five of eight patients with T_3 tumours, the sentinel node was involved. Even in these patients, the sentinel node indicated nodal status accurately. The sentinel node was the only positive node in 22 of the 37 sentinel node-positive patients. In 33 of the 37 patients, the metastasis was seen in the hottest sentinel node. However, in four patients the hottest sentinel node was clear, although metastasis was found in another sentinel node. In these patients, mean positive sentinel node radioactivity was 41·5 (range 15·2–74·6) per cent of the hottest sentinel node reading. These four patients had a mean tumour size of 2·4 cm. Multicentricity, tumour size and site did not affect this phenomenon.

Discussion

Sentinel node biopsy is now emerging as a useful technique, but there is currently no standard identification technique. At present, either a dye, a radiocolloid, or both, is used for sentinel node biopsy in patients with breast cancer[2,4,5,11]. Generally, radiocolloid localization seems to detect sentinel nodes more frequently than vital blue dye; the combination may be the best[15]. However, Veronesi *et al.*[16] reported excellent results with radiocolloid alone.

Radiocolloid characterization encompasses several physical, chemical and radiochemical parameters. Physical parameters comprise particle size and activity size distributions, particle shape, particle concentration and stability[17]. The lymphatic collection process is strongly related to particle size. Particles smaller than 4–5 nm will penetrate capillary membranes and therefore may not migrate through the lymphatic channel. Particles larger than 4–100 nm show the most rapid dispersal from interstitial space into lymphatic vessels, yet have significant retention in the lymph node. Particles larger than 500 nm have a much slower rate of clearance from the interstitial space with significantly less accumulation in lymph nodes. After migration from the interstitial space to the lymphatic vessels, particles are moved to lymph nodes, where they can be retained by mechanical trapping or phagocytosis[1,17–20].

Commonly used radiocolloids in Europe and North America are technetium-99m colloidal albumin and technetium-99m sulphur colloid. Success rates reported for identifying sentinel node with radiocolloid alone are 88–99 per cent[7,10,11,16,21]. Particle sizes of these radiocolloids are: colloidal albumin (less than 80 nm (Nanocoll, Sorin Biomedica Diagnosis, Saluggia, Italy) and 200–1000 nm (Albu-Res, Sorin Biomedica Diagnosis, Saluggia, Italy)) and sulphur colloid (200–1000 nm)[22]. This study used technetium-99m colloidal rhenium sulphide with particle size 50–200 nm.

Schneebaum *et al.*[23] reported sentinel node biopsy results using technetium-99m colloidal rhenium sulphide in 30 patients with breast cancer. Two patients who had previously undergone radiation treatment had negative lymphoscintigraphy findings. In the remaining 28 patients lymphoscintigraphy was positive and the sentinel node was identified in all patients. As no patient underwent preoperative radiotherapy in the present study, these data would support the present results.

The positive rate of lymphoscintigraphy is strongly related to the sentinel node identification rate. When lymphoscintigraphy reveals an axillary hot spot, the sentinel node is identified easily with a γ probe at operation. Lymphoscintigraphy-positive rates of sulphur colloid, Nanocolloid and Albres were reported as 75 per cent[11], 89 per cent[10] and 99 per cent[16] respectively. Furthermore, sentinel node identification rates for these radiocolloids were 88 per cent[11], 94 per cent[10] and 99 per cent[16]. This demonstrates that the type of radiocolloid affects the sentinel node identification rate. In the present study the lymphoscintigraphy-positive rate was 100 per cent, suggesting that colloidal rhenium sulphide is particularly suitable for sentinel node mapping in breast cancer.

A major problem with sentinel node biopsy is the false-negative indication; fortunately, none occurred in this study. The mechanism of false-negative indication is still unknown. In four of 37 patients with a positive sentinel node in this study, hottest node was negative and other hot node was involved with tumour. Multicentricity, tumour size and site did not affect this phenomenon. Martin *et al.*[24] reported similar findings in sentinel node biopsy using sulphur colloid and isosulfan blue dye. The authors reported that, if only the hottest node had been removed, the false-negative rate would have been 13 per cent. This suggests that the hottest node is not always the true sentinel node; alternatively, when a tumour has more than one sentinel node, metastases do not always occur in the hottest sentinel node. De Cicco *et al.*[25] reported that small particle colloids (less than 50 nm) were often trapped in several nodes, whereas larger particle colloids (200–1000 nm) were often taken by one node only. If a larger particle radiocolloid were to be used, positive sentinel nodes might not be identifiable with a γ probe because of low radioactivity. This study defined the sentinel node as a node with more than 10 per cent of the radioactivity of the hottest node; 182 sentinel nodes in 87 patients were identified. These sentinel nodes included true sentinel nodes and second or higher-echelon nodes. A method that identified only true sentinel nodes would be best.

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Original article

Unique clinical characteristics of primary hyperparathyroidism in India

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Background: The features of primary hyperparathyroidism (PHPT) in developing countries have rarely been examined. This study explored the clinical characteristics of PHPT in India with the hypothesis that this may improve understanding of the pathogenesis of the disease worldwide.

Methods: Consecutive patients with PHPT (24 women, five men) were examined prospectively before and after parathyroidectomy.

Results: All patients had osteitis fibrosa cystica with a median symptom duration of 2·5 (range 1–26) years. Single or multiple fragility fractures were present in 14 patients (eight were bedridden); 20 had brown tumours. Mean preoperative serum calcium was 3·1 mmol/l, while mean serum intact parathyroid hormone (iPTH) and total alkaline phosphatase (ALP) levels were 17-fold and 12-fold higher than normal respectively. Nine patients had overt renal damage, mainly nephrocalcinosis. Parathyroidectomy invariably resulted in severe hypocalcaemia, necessitating long-term vitamin D treatment. The mean parathyroid gland weight was 8·6 (range 2·0–36·6) g and features of carcinoma were found in four patients. Serum calcidiol level correlated inversely ($P < 0.05$) with serum iPTH and ALP, and parathyroid gland weight.

Conclusion: PHPT in Indians is a severe, symptomatic disorder with skeletal, muscular and renal manifestations at a young age. The presence of this severe variant of PHPT in vitamin D-sufficient Indians, and the lack of skeletal disease in other vitamin D-deficient populations, raises the possibility of additional pathogenetic factors.

Presented to the Millennium Meeting of the British Association of Endocrine Surgeons, London, UK, May 2000

Paper accepted 16 January 2001

British Journal of Surgery 2001, 88, 708–714

Introduction

Primary hyperparathyroidism (PHPT) is usually diagnosed at an asymptomatic stage in the western world; patients are generally elderly and lack overt skeletal and renal manifestations[1,2]. For many such patients surveillance alone has been recommended[3]. Parathyroid adenoma weighing up to 1 g is the characteristic cause of the disease and, following its successful removal, patients rarely require treatment for hypocalcaemia[4,5]. Large adenomas and parathyroid carcinoma are rarely encountered[6]. The pathogenesis of PHPT is poorly understood. Consistent somatic mutations in the parathyroids and irradiation of the neck are demonstrable in only a fraction of patients[7,8]. Deficiency of vitamin D has been considered a contributory cause[9] but it may be clinically occult and relate to altered expression of the parathyroid vitamin D receptor[10,11].

In developing countries, the clinical and pathological characteristics in the few reports of patients with PHPT[12–17] mirror those found in the west several decades ago. The patients are young and present with symptomatic skeletal and renal manifestations due to palpable, and not infrequently malignant, parathyroid tumours[12–17]. Some of these patients have crippling muscular weakness, osteitis fibrosa cystica (OFC) and multiple fractures[12].

Vitamin D nutrition is an important factor determining the severity of skeletal disease and parathyroid growth, and could be an important pathogenetic mechanism in this variant of PHPT[9,18]. However, the absence of OFC in vitamin D-deficient patients with PHPT in the western world[9,18] and the presence of severe skeletal disease even in vitamin D-sufficient Indian patients suggests the possibility of a more complex sequence of pathogenetic events.

Patients and methods

Twenty-nine consecutive patients with PHPT were managed at Sanjay Gandhi Postgraduate Institute of Medical Sciences Hospital, Lucknow, India during 1990–1998. Evaluation of the patients included measurement of serum total and ionized calcium, inorganic phosphorus, total alkaline phosphatase (ALP), intact parathyroid hormone (iPTH), calcidiol and calcitriol. Radiological survey included the hands, skull, lumbar spine, pelvis and any suspected or known sites of fractures and brown tumours. Plain films were taken to diagnose renal stones or nephrocalcinosis. Bone mineral density (BMD) at the forearm, lumbar spine and hip was measured by dual energy radiographic absorptiometry (Hologic 4500 QDR; Hologic Inc., Bedford, MA, USA) in the last 14 patients. An equal number of age- and sex-matched healthy controls also underwent measurement of BMD, and serum calcidiol and calcitriol levels.

Patients underwent bilateral neck exploration under general anaesthesia with a conventional strategy of parathyroidectomy. This involved visual identification of at least four parathyroid glands, achieved in 22 of 29 patients, and removal of enlarged glands. Biopsy of one normal looking parathyroid gland was carried out in 21 patients. All excised material was examined microscopically using conventional histological criteria[19]. Serum calcium was estimated daily after parathyroidectomy. Postoperative hypocalcaemia was managed by calcium gluconate infusion (1–2 mg per kg per h) and oral calcium carbonate and calcitriol (0·5–1·5 µg/day). Patients were discharged 7–10 days following surgery after achieving normocalcaemia on oral calcium and vitamin D supplementation. Patients were followed up for a median duration of 42 (range 16–122) months. Clinical and biochemical evaluations were carried out at every follow-up visit, while radiological and densitometric evaluations were done every 6 months.

Fasting serum calcium and phosphorus, and 24-h urinary calcium excretion were determined with an autoanalyser, while serum total ALP levels were assayed using the Jaffe method. Serum iPTH levels were measured using an immunoradiometric assay (DSL, Webster, TX, USA), and calcidiol and calcitriol by radioimmunoassay (Incstar, Still Water, MN, USA). Normal ranges of the biochemical indices are shown in *Table 1*.

Correlations were investigated with Spearman's rank order correlation coefficient and groups were compared with the Wilcoxon signed rank test. A probability of less than 5 per cent was considered significant. Values are displayed as the median or as the arithmetic mean and range.

Results

The mean age of the 29 patients (24 women, five men) was 38 (range 13–60) years; three were younger than 18 years. PHPT was apparently sporadic in all but one patient with multiple endocrine neoplasia type I. All the patients had symptoms attributable to PHPT, although two were detected fortuitously during investigation for an unrelated disorder.

Symptoms and signs

The median duration of symptoms was 2·5 (range 1–26) years, and all patients had generalized bone pain. Eight patients were bedridden owing to multiple fractures, deformities from expanding brown tumours or severe muscular weakness. Fourteen patients had suffered single

Table 1 Biochemical indices in patients with primary hyperparathyroidism

	Normal range	Before operation	After operation			
			1 day	7 days	3 months	6 months
Serum						
Calcium (mmol/l)	2·1–2·6	3·1 (2·4–3·7)	1·7 (1·4–2·0)	2·1 (1·7–2·4)	2·3 (2·2–2·5)	2·2 (2·2–2·6)
Inorganic phosphorus (mmol/l)	1·1–1·8	0·7 (0·5–1·0)	0·8 (0·6–1·1)	1·0 (0·9–1·2)	1·5 (1·3–1·9)	1·3 (1·2–1·8)
ALP (units/l)	< 125	1544 (177–7240)	1890 (340–6987)	1994 (345–7235)	684 (257–2312)	645 (232–1721)
iPTH (pmol/l)	1·1–5·8	82·7 (14·1–194·8)	1·3 (< 1·1–7·8)	3·0 (1·1–7·4)	4·0 (2·5–5·9)	4·1 (3·0–5·2)
Creatinine (mmol/l)	53–132·6	79·6 (53–282·8)*	–	–	–	–
Calcidiol (nmol/l)	22·1–111·9	33·8 (15·4–62·2)	–	–	–	–
Calcitriol (pmol/l)	23·1–121	110·9 (61·6–189·2)	–	–	–	–
Urine						
Calcium (mmol per 24 h)	< 5·1	4·6 (2·0–8·0)	–	–	–	–

Values are mean (range). *Serum creatinine level was high in two patients, both with bilateral nephrocalcinosis. ALP, alkaline phosphatase; iPTH, intact parathyroid hormone

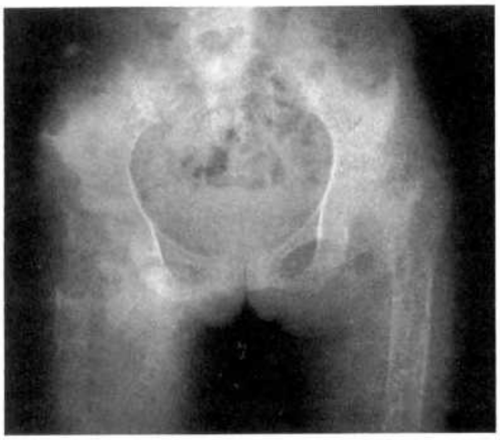

Fig. 1 Radiograph of the pelvis (anteroposterior view) showing extreme osteopenia, brown tumours of the femur and fractures

or multiple fragility fractures, three of whom were unaware of these before radiological examination. Twenty patients had brown tumours, which were clinically evident in seven as bony swellings or deformities. Significant proximal muscular weakness was present in 21 patients. Nine patients had renal involvement in the form of calculi or nephrocalcinosis; four were symptomatic. Twelve patients had significant behavioural problems, depressive psychoses in five being the commonest. Clinically evident anaemia was present in 23 patients. Other noticeable clinical features were restrictive respiratory disease in almost half of the patients, possibly related to respiratory muscle weakness, a thin dry skin and oral ulcers. Toothache, in the absence of any inflammatory dental pathology, was another noticeable feature, present in 12 patients, and could have been a part of generalized bone pain.

Biochemistry, radiology and bone densitometry

Total serum calcium levels before parathyroidectomy ranged from 2·4 to 3·7 mmol/l, despite serum iPTH levels being extremely high (mean 82·7 pmol/l) in most patients (*Table 1*). No linear correlation could be detected between serum calcium and serum iPTH. One patient had normocalcaemic PHPT (serum calcium 2·4 mmol/l, iPTH 34·6 pmol/l), overt OFC but no renal impairment. Urinary excretion of calcium was not abnormal in the majority of the patients. The high serum iPTH level was unrelated to renal impairment, since only two patients with bilateral nephrocalcinosis had a high serum creatinine level. Serum calcidiol levels were subnormal or low normal in the patients with PHPT and were higher than those in controls ($P > 0·05$). Serum calcitriol levels were high normal in patients with PHPT, significantly higher than those in controls ($P < 0·05$). Negative correlations were observed between serum calcidiol and serum iPTH ($P < 0·001$), ALP ($P < 0·05$) and parathyroid gland weight ($P < 0·05$). There was a trend towards a positive relationship between serum calcidiol and BMD at the radius and the lumbar spine ($P = 0·09$).

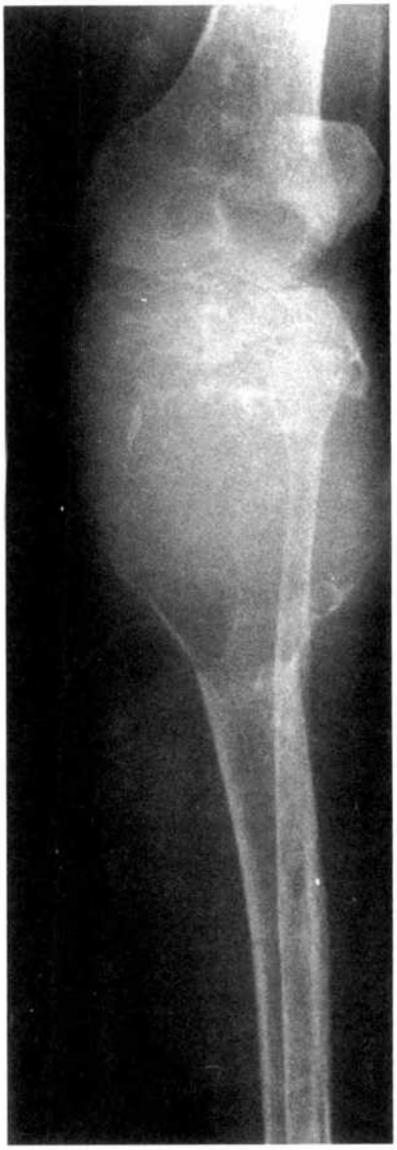

Fig. 2 Brown tumour of the upper end of the tibia

All patients had radiological features of OFC, namely subperiosteal bone resorption, cortical cysts and osteopenia. The spine, pelvis (*Fig. 1*), thighs and legs demonstrated extreme osteopenia, bone cysts, brown tumours and fractures (*Fig. 2*). Mean BMD *Z*-scores at the distal radius and lumbar spine were − 4·2 and − 3·8 respectively (*Table 2*). Interestingly, BMD was substantially low both at trabecular (wrist) and cancellous (hip and spine) bone sites.

Parathyroid surgery and histology

A single parathyroid adenoma was found in 20 patients, one had a double adenoma and four had primary parathyroid hyperplasia which was nodular and asymmetric in three. Biopsies of all assumed normal parathyroid glands in 21 patients were reported as normal or suppressed glands on histological examination. *En bloc* resection of a parathyroid tumour was carried out in five patients with intraoperative suspicion of carcinoma in view of gross tumour invasion. One of these was eventually diagnosed as an adenoma. The diagnosis of parathyroid carcinoma was based on the presence of gross capsular and vascular invasion, wide fibrovascular septae, cellular and nuclear pleomorphism and a high mitotic index. In addition, two of three patients subsequently developed metastases. The mean total parathyroid gland weight was 8·6 (range 2·0–36·6) g, and 13 adenomas measured more than 2 cm in diameter. No distinctions in clinical, biochemical and radiological features could be made between patients with parathyroid adenoma, hyperplasia or carcinoma. A higher parathyroid gland weight, however, was noted for carcinoma (mean 21·0 g) than for adenoma (7·9 g) and hyperplasia (3·7 g) ($P < 0{\cdot}005$).

Postoperative course and outcome

All of the patients suffered early, symptomatic hypocalcaemia after parathyroidectomy (*Table 2*). Serum calcium levels fell to a trough within a mean of 28 (range 17–33) h. Intravenous calcium gluconate was maintained for a median of 6 (range 3–8) days. Perioperative complications (30 days) included septicaemia in three patients; two developed pancreatitis and died 7 and 10 days after operation with multiple organ failure. One patient had serious staphylococcal pneumonia and two others had fever of unknown origin. No patient sustained recurrent laryngeal nerve palsy, wound infection or haemorrhage requiring reoperation.

All had relief of bone pain within 48 h of parathyroidectomy. The other dramatic recovery was of muscular weakness, which led to all the bedridden patients without unstable fractures being able to stand. Serum calcium and iPTH levels were normal at 6 months' follow-up in all patients (*Table 2*). One patient with a parathyroid adenoma and bilateral nephrocalcinosis had a slightly raised early postoperative iPTH level, but this settled to normal within 6 months of follow-up. None of the 25 patients with benign parathyroid pathology has developed recurrent hyperparathyroidism during follow-up ranging from 16 to 122 months.

Table 2 Bone mineral densitometric findings in the 14 most recent patients with primary hyperparathyroidism and matched controls

	PHPT (*n* = 14)		Controls (*n* = 14)
Site	BMD* (g/cm²)	*Z*-score	BMD* (g/cm²)
Distal third radius	0·370	− 4·2	0·541
Total hip	0·429	− 2·9	0·804
Lumbar spine (lateral)	0·425	− 3·8	0·813
Whole body	0·717	− 3·2	1·031

*Values are mean. BMD, bone mineral density; PHPT, primary hyperparathyroidism

One of the patients with parathyroid carcinoma died perioperatively from pancreatitis and septicaemia. Two patients with parathyroid carcinoma presented with recurrent PHPT due to metastases 28 and 58 months after parathyroidectomy. One died from respiratory failure and multiple intracranial metastases; the other developed metastatic contralateral neck nodes. The latter patient also had chronic renal failure due to progressive bilateral nephrocalcinosis. The final patient with an intrathyroidal parathyroid carcinoma was a 19-year-old girl who was bedridden owing to extreme osteopenia and multiple fractures; she is alive and well, with no signs of recurrent tumour 4·5 years after parathyroidectomy.

Discussion

PHPT is common in developed countries, and there are recent indications of a decrease in its incidence in North America and Sweden[2,20]. The prevalence rises with age for both sexes, and postmenopausal western women are particularly susceptible[2,21]. Most patients lack overt symptoms and are detected fortuitously[1]. Lack of symptoms and the indolent nature of the disorder have led to a conservative attitude[3,22,23]. The vague symptoms can impair quality of life but are difficult to evaluate objectively[24–26]. Parathyroidectomy can reduce the risk of cardiovascular disease and premature death in patients with PHPT[27,28].

This contrasts to the 'bone, stones, moan and groans' presentation of PHPT during the first half of the past century. This change has been attributed to the advent of biochemical screening. Early detection may prevent progression to more florid disease. This contrasts with the rarity of progressive hypercalcaemia, renal impairment and OFC during decades of surveillance[18,21,29]. It also seems unlikely that increased awareness alone could account for the shift from the third/fourth to the fifth/seventh decades of life for the peak incidence of PHPT[1].

The clinical picture of PHPT in India today is similar to that recognized previously in the west. The disease is seemingly rare, patients are comparatively young, and they suffer overt skeletal and renal manifestations[12,13]. Similar clinical and pathological features of this disease have been reported from other developing countries[14–17].

Symptomatic OFC and a severely decreased BMD were dominant manifestations of PHPT[12–17]. This contrasts with the mild-to-moderate cortical osteopenia and sparing of cancellous bone in PHPT of western societies[30–32]. The tremendous loss of bone mineral both at cortical and cancellous sites in the present series was accompanied by multiple fractures. Other unusual observations were the large, multiple brown tumours causing gross deformity and spontaneous fracture. The upper tibia and pubic rami were the most common sites of fractures and brown tumours, while unusual sites included the vertebral body, iliac crest, hard palate and ribs.

The patients had extremely high serum iPTH and ALP levels, which signify deranged secretory control in very large parathyroid glands and the severity of bone involvement. Consistent with other studies, however, the extent of hypercalcaemia was moderate and a few patients were actually normocalcaemic[12–15]. This may be due to vitamin D insufficiency, low dietary calcium intake and poor bone mineral reserve. These circumstances reflect a substantial calcium resistance to PTH secretion, which is a rather poorly understood phenomenon related to the calcium-sensing ability of the parathyroid cells, and the effects of calcitriol[9,33]. The unusual relationship between serum calcium and iPTH also underlines the peripheral resistance to the calcaemic actions of PTH, which can relate to loss of the protective effects of calcitriol mainly in bone, and the defective actions of the PTH receptor[1,18]. Another characteristic feature was the impressive size of the parathyroid glands; one-third of the benign parathyroid tumours were palpable at diagnosis. A common pathogenic denominator in all these respects is calcitriol, since it also seems to be the most potent inhibitor of parathyroid gland growth[34].

There was a high incidence of parathyroid cancer in the present small series. Extreme biochemical indices of PHPT, severe skeletal and renal involvement, and palpable parathyroid tumours are considered predictors of parathyroid carcinoma[4,5]. Besides a greater tumour weight, however, there were no discernible clinical differences between parathyroid adenoma and carcinoma in the present series.

The postoperative interval was far from uneventful. Infection was a principal problem and may have been related to impaired cellular and humoral immunity from high serum iPTH levels[35]. There was invariably a marked postoperative hypocalcaemia that started early and required sustained vitamin D supplementation, most likely due to 'hungry bone syndrome'. There were signs of renal damage in only two of the patients with bilateral nephrocalcinosis. Parathyroidectomy resulted in marked, early and sustained, although varied and disorderly, remineralization of the diseased skeleton in all patients[36].

Serum calcidiol has been suggested as one of the determinants of the extent of parathyroid growth and the severity of bone loss in PHPT in countries in which vitamin D deficiency is a public health problem[1,9,12,13,18]. The serum calcidiol level was subnormal or low normal in the present series, and the rise in serum calcitriol was very modest, considering the extent of the PTH excess. The importance of calcidiol was supported by its negative correlation to parathyroid tumour weight, serum iPTH and ALP levels, and a trend to a similar relationship with BMD. Differences in vitamin D nutrition and delay in seeking medical advice could account for much of the geographically heterogeneous presentation of PHPT[12,13,17]. It is not known whether this severe PHPT variant is coupled to the presence of a hidden milder 'western' type of disease, since population-based analyses are lacking in vitamin D-deficient countries. In American patients with PHPT and a vitamin D insufficiency, however, the biochemical, densitometric and histomorphometric indices of skeletal manifestations and parathyroid tumour growth are far milder than those in India[9,18]. The existence of similarly severe skeletal manifestations in the rare vitamin D-replete Indian patients with PHPT also suggests that factors other than vitamin D interact in the development of PHPT in India and other developing countries.

Acknowledgements

The authors are grateful to Dr D. S. Rao of Henry Ford Medical Systems, Detroit, USA for helping with vitamin D assay of the earlier seven patients. The authors thank Dr A. K. Singh, Dr V. Arya and Dr A. Agarwal for collection and analysis of part of the data, and to all faculty Staff and residents of the Endocrine Sciences Center, Sanjay Gandhi Postgraduate Institute of Medical Sciences, for providing the clinical care to patients.

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Original article

Prospective analysis of the diagnostic yield of extended *en bloc* resection for adenocarcinoma of the oesophagus or gastric cardia

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Background: The extent of lymph node dissection can affect tumour node metastasis staging. The resulting 'stage migration' might hamper stage-by-stage comparison between different forms of oesophageal resection. The aim of this study was to assess the diagnostic impact of extended *en bloc* lymphadenectomy in staging (adeno)carcinoma of the mid/distal oesophagus or gastric cardia.

Methods: This was a prospective study of 74 patients (67 men and seven women; median age 63 (range 40–78) years) who underwent extended oesophagectomy between 1994 and 2000.

Results: A median of 31 (range 15–78) lymph nodes was resected (and identified), with a median of 5 (range 0–31) positive nodes. Twenty-seven patients (36 per cent) had tumour-positive nodes in extended fields: 15 patients (20 per cent) in the abdomen and 15 patients (20 per cent) in the mediastinum. Subcarinal nodes were most affected (19 per cent). Extended resection led to tumour upstaging in 17 patients (23 per cent); two patients had isolated positive subcarinal nodes and 15 other tumours became M_{1a} owing to positive nodes near the coeliac axis, hepatic artery or splenic artery. Tumour positivity in paratracheal or aortopulmonary nodes occurred in 8 per cent of patients, without influencing staging.

Conclusion: Extended *en bloc* lymphadenectomy altered staging in 17 of 74 patients (23 per cent) with adenocarcinoma of the oesophagus or cardia, mainly into M_{1a} owing to positive coeliac nodes (20 per cent).

Presented in abstract form to United European Gastroenterology Week, Brussels and the British Association of Surgical Oncology, London, November 2000

Paper accepted 6 December 2000

British Journal of Surgery 2001, 88, 715–719

Introduction

Lymph node dissection for oesophageal carcinoma serves three purposes: it aids in the staging of the disease, it may decrease or postpone the incidence of locoregional tumour recurrence, and it may prolong (disease-free) survival. Proper staging offers important prognostic information, for both physician and patient, and might influence the decision to apply adjuvant chemotherapy and/or radiation therapy.

During a transhiatal oesophageal resection, the left gastric artery is transected as it branches from the coeliac axis, and only nodes at the origin of the left gastric artery are removed routinely. Nodes near the coeliac axis (i.e. nodes near the hepatic and splenic arteries and the coeliac axis itself) are not resected routinely. Metastases in these nodes are considered distant metastases (M_1) for oesophageal carcinoma according to the Union Internacional Contra la Cancrum (UICC) 1997 tumour node metastasis (TNM) classification[1]. The subcarinal lymph nodes are also not included in the resection during a transhiatal procedure. The positivity of these nodes affects the N status, but not the M status.

In general, variability in the extent of lymph node dissection and number of lymph nodes examined per lymph node station can significantly affect nodal staging and thus TNM staging. This can lead to so-called stage migration, i.e. the migration of disease into a more advanced stage, by demonstrating (more distant) lymph node metastases, which would not have been identified by a less extended lymphadenectomy. This phenomenon might hamper the stage-by-stage comparison between different forms of oesophageal resection. In this study the effect of an extended *en bloc* resection on staging adenocarcinoma of the mid/distal oesophagus or gastric cardia was evaluated.

Patients and methods

Patients undergoing right-sided transthoracic oesophagectomy with an extended *en bloc* lymph node dissection for adenocarcinoma of the mid/distal oesophagus or gastric cardia, as part of a randomized trial comparing transhiatal resection with transthoracic oesophagectomy with extended *en bloc* lymph node dissection, were enrolled. Operations were performed with curative intent, that is in the absence of local irresectability and/or distant metastases (including positive cervical lymph nodes or irresectable coeliac lymph nodes).

The diagnostic evaluation consisted of endoscopy with biopsy, endosonography, external sonography of abdomen and neck, and laryngoscopy to evaluate the function of the vocal cords. Routine chest radiography and electrocardiography were also performed. Laparoscopy with laparoscopic ultrasonography was added for carcinoma of the cardia. The latter was defined as a lesion with the tumour bulk at or distal to the gastro-oesophageal junction as determined endoscopically or endosonographically.

The TNM classification of the UICC (1997) was used for staging[1]. Oesophageal carcinoma and carcinoma of the cardia (with substantial ingrowth in the oesophagus) were considered as one clinical entity and staged by the classification for oesophageal carcinoma[2]. Nodes near the coeliac axis, the hepatic artery and the splenic artery were considered to be M_{1a}. Histologically proven tumour-positive lymph nodes in the neck (M_{1b}) were considered to be a contraindication to curative surgery, while resectable enlarged lymph nodes near the coeliac axis (formally M_{1a}) were not.

All patients underwent a cervicothoracoabdominal subtotal oesophageal resection with dissection of the right-sided paratracheal (up to 3 cm from the subclavian artery, leaving the right recurrent nerve chain *in situ*), aortopulmonary window, subcarinal, mediastinal, paracardial, lesser and greater curvature, left gastric artery, common hepatic artery, splenic artery and coeliac trunk lymph nodes. The left paratracheal/recurrent laryngeal nerve chain was not dissected. Paratracheal, aortopulmonary window and subcarinal lymph nodes were considered to be extended lymph nodes, as were nodes near the hepatic artery, near the splenic artery or near the coeliac trunk. Nodes at the origin of the left gastric artery were not considered to be extended nodes, as they are also removed during non-extended transhiatal resection without formal lymph node dissection. The anastomosis was made in the neck, approaching the neck from the left side for reasons described elsewhere[3]. No formal lymphadenectomy was performed in the neck.

Surgery was performed or supervised by one of three experienced oesophageal surgeons at tertiary care centres with a wide experience in oesophageal surgery (more than 70 resections each annually).

The origin of the left gastric artery and the subcarinal nodes was marked in the resection specimen. Separate lymph nodes were marked by localization and submitted in separate bottles. Perioesophageal tissue and lesser and greater omentum were palpated for the presence of lymph nodes by the pathologist, and subsequently dissected. Routine staining was performed using a standardized protocol in which lymph nodes were bisected and both sides were stained with haematoxylin and eosin. Patients were only eligible for the present study when 15 or more lymph nodes had been resected and identified by the pathologist, and the subcarinal and left gastric artery lymph nodes were marked adequately. The resection specimens were reviewed by an experienced (gastrointestinal) pathologist, and pathological findings were described on a standardized form. The pathological (pTNM) stage, tumour diameter, differentiation grade, radicality, total number of resected lymph nodes and total number of positive lymph nodes, including their localization, were recorded. No additional immunohistochemical staining techniques to detect micrometastases were used.

Results

Between 1994 and 2000, 74 patients who met the inclusion criteria underwent extended transthoracic oesophagectomy: 67 men and seven women with a median age of 63 (range 40–78) years. This group accounted for 75 per cent of all patients undergoing transthoracic resection with extended *en bloc* resection in the study period. There were 60 tumours of the distal oesophagus (81 per cent) and 14 tumours of the cardia (19 per cent). Median operation time was 6 (range 3·5–8·5) h. The in-hospital mortality rate was 7 per cent (five of 74 patients). The median stay in intensive/high-dependency care was 6 (range 1–79) days and the median hospital stay was 22 (range 7–154) days.

The median number of resected and identified lymph nodes per patient was 31 (range 15–78), with a median number of 5 (range 0–31) histologically positive nodes. There were no positive lymph nodes found in nine patients with T_1 tumours (all submucosal) while lymph node metastases were found in nine of nine and 50 of 56 patients with T_2 and T_3 tumours respectively. The distribution of lymph nodes is shown in *Table 1*. Tumour-positive lymph nodes were most frequently encountered in the non-extended fields. Overall, 27 patients (36 per cent) had positive lymph nodes in extended resection fields: 15 patients (20 per cent) had positive nodes in the extended fields of the mediastinum and 15 patients (20 per cent) had positive nodes in the extended fields of the abdomen. Three patients had positive nodes in the extended fields of both abdomen and chest. There was no difference between oesophageal carcinoma and carcinoma of the cardia regarding the presence of nodal metastases in the extended fields.

The pTNM stage of the tumours is shown in *Table 2*. An extended resection in the chest and abdomen led to upstaging of the tumour in 17 (23 per cent) of 74 patients, 14 of 60 patients with oesophageal carcinoma and three of 14 patients with carcinoma of the cardia. Two of these 17 patients had isolated positive subcarinal nodes, upstaging from N_0 to N_1. The remaining 15 patients had M_{1a} nodes in the abdomen: positive (resectable) lymph nodes near the coeliac axis, near the hepatic artery or near the splenic artery. Eight patients had positive nodes near the coeliac axis without positive nodes at the origin of the left gastric artery. There was no upgrading due to tumour-positive paratracheal or aortopulmonary nodes, although in three patients these were the only positive node locations in the chest (but the patients also had positive nodes in the non-extended abdominal fields).

Discussion

In the present series, tumour-positive lymph nodes in the extended fields changed staging in 17 (23 per cent) of 74 patients, offering potentially important diagnostic and prognostic information. This stage migration has been demonstrated clinically for gastric carcinoma, but not as yet for oesophageal carcinoma[4,5].

During routine transhiatal resection at the authors' institutions the nodes near the origin of the left gastric artery are removed. Adding a formal dissection near the coeliac axis changed staging in 20 per cent of patients. Eight of these patients showed some form of skip metastases, nodes near the coeliac axis being positive without positive

Table 1 Lymph node distribution among 74 patients with adenocarcinoma of the mid/distal oesophagus and/or gastric cardia who underwent extended lymphadenectomy in the chest and abdomen

	No. of patients		
Lymph node station	Lymph nodes identified	Lymph nodes positive	Positive/removed*
Paratracheal/aortopulmonary	61 (82)	6 (8)	0·10
Subcarinal	69 (93)	14 (19)	0·20
Mediastinal/paracardial	68 (92)	35 (47)	0·52
Lesser curvature	58 (78)	37 (50)	0·64
Origin of left gastric artery	57 (77)	27 (36)	0·47
Hepatic/splenic artery/coeliac axis	53 (72)	15 (20)	0·28

Values in parentheses are percentages. *Ratio of positive to removed and identified lymph nodes

Table 2 Pathological tumour node metastasis (pTNM) stage of tumours in 74 patients after extended *en bloc* resection compared with pTNM stage when only non-extended lymph node stations were taken into account

	Extended *en bloc* resection					
	Stage I	Stage IIa	Stage IIb	Stage III	Stage IV	Total
Non-extended resection						
Stage I	9	–	–	–	–	9
Stage IIa	–	5	1	1	1	8
Stage IIb	–	–	6	–	2	8
Stage III	–	–	–	37	12	49
Stage IV	–	–	–	–	0	0
Total	9	5	7	38	15	74

nodes near the origin of the left gastric artery. A formal lymphadenectomy near the coeliac axis can probably be done without increasing morbidity or mortality rates substantially, and provides important diagnostic information. Based on this assumption, a routine lymph node dissection might be recommended for staging purposes in the upper abdomen, if this diagnostic information leads to an altered postoperative adjuvant strategy.

During a transthoracic *en bloc* resection the subcarinal (and sometimes the lower paratracheal) nodes are removed routinely, while the nodes in the aortopulmonary window are not dissected. In the present protocol the nodes in the aortopulmonary window were resected together with the right-sided paratracheal nodes, which led to the term 'extended *en bloc*' resection.

The subcarinal nodes were positive in 19 per cent of patients. This is in accordance with the literature, in which the percentage of patients with positive nodes ranges from 10 to 40 per cent[5–8]. These nodes might sometimes be reached through the widened hiatus of the diaphragm during transhiatal resection, but this would require the use of large retractors, possibly leading to more manipulation of the heart, and dissection under suboptimal vision. In routine transhiatal resection, these nodes are therefore only rarely removed. Although not important for staging (stage in only two patients (3 per cent) changed from N_0 to N_1 owing to isolated positive subcarinal nodes), the large percentage of tumour-positive lymph nodes at this site suggests a possible benefit of routine clearance of the subcarinal nodes. Whether or not removal of these positive subcarinal nodes lowers the incidence of locoregional recurrence and perhaps even improves long-term survival is beyond the scope of the present analysis. Adding a thoracotomy probably increases the physiological impact of the operation, leading to increased postoperative morbidity and mortality rates[9,10]. Therefore, adding a formal thoracotomy for staging purposes only seems unwarranted based on the present data.

Some authors propose using a classification system in which adenocarcinoma of the distal oesophagus and adenocarcinoma of the gastric cardia are considered as one entity[2,11]. In the present paper the TNM classification for carcinoma of the distal oesophagus was used. There seemed to be no difference in lymph node spread between oesophageal carcinoma and carcinoma of the cardia. However, when the TNM classification of stomach cancer is used, the nodes located along the left gastric, common hepatic, splenic and coeliac arteries and the hepatoduodenal nodes are considered as regional lymph nodes, and not as distant metastases. Only involvement of other intra-abdominal lymph nodes such as the retropancreatic, mesenteric and para-aortic nodes is classified as constituting distant metastasis. In the present series, dissection of these latter nodes was not performed. If the stomach cancer criteria were applied to the lymph nodes in the abdomen, there would not have been any stage migration due to removal of the peritruncal nodes. However, 28 tumours (38 per cent) would have been restaged as M_1 owing to the presence of intrathoracic nodal disease as a thoracic lymph node dissection would have been performed.

Less invasive (non-operative) techniques are being developed to supply more accurate diagnostic information about the status of specific lymph node stations. When combined with fine-needle aspiration, endosonography might, in experienced hands, be able to reliably identify patients with cytologically positive nodes[12–14]. When the subcarinal or paratracheal nodes are found to be positive, an *en bloc* resection might be considered. However, even with experience, it is difficult to distinguish between nodes near the origin of the left gastric artery (N_1) and nodes near the coeliac axis (M_1), which is why only the presence of enlarged, irresectable (more than 2 cm on external ultrasonography), histologically proven tumour-positive nodes near the coeliac axis was used as a contraindication to surgery in the present study. In this series, there was one patient with endosonographically suspicious nodes near the coeliac axis undergoing resection; in the other 14 patients the presence of nodal metastases became apparent in the resection specimen. Laparoscopy in combination with laparoscopic ultrasonography, performed only in patients with carcinoma of the cardia, had not been able to detect these small metastases. The development of positron emission tomography and magnetic resonance imaging with iron contrast might also aid in the preoperative staging of patients with carcinoma of the oesophagus[15–18]. However, until long-term recurrence and survival data are available, the therapeutic effect of a more extended lymphadenectomy remains uncertain.

An extended lymphadenectomy in the abdomen and chest altered staging in 23 per cent of patients with (adeno)carcinoma of the mid/distal oesophagus and/or gastric cardia, offering valuable diagnostic and prognostic information. Stage migration in oesophageal cancer occurred mainly due to positive nodes in the upper abdomen. If dissection of these nodes can be performed without increasing morbidity or mortality rates substantially, a routine extended lymphadenectomy along the coeliac axis can be recommended for staging purposes. Although often positive, subcarinal nodes changed staging only in a small minority of patients. Routine clearance of the subcarinal nodes, requiring a thoracotomy or a technically demanding extended transhiatal resection, is probably not warranted for staging purposes only. Less invasive preoperative diagnostic modalities may identify patients with positive subcarinal or paratracheal nodes, but whether removal of these nodes offers any (disease-free) survival benefit has yet to be demonstrated.

Acknowledgements

The authors thank Dr B. P. L. Wijnhoven (Department of Surgery, University Hospital Rotterdam – Dijkzigt), Dr P. Fockens (Department of Gastroenterology, Academic Medical Center/University of Amsterdam) and Dr F. J. W. ten Kate (Department of Pathology, Academic Medical Center/University of Amsterdam) for assistance in obtaining the data presented in the study and critical comments during preparation of the manuscript.

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Original article

Contralateral groin exploration is not justified in infants with a unilateral inguinal hernia

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Background: In children undergoing a unilateral inguinal herniotomy, the contralateral groin is often explored on the basis of a high incidence of patency of the processus vaginalis. The patency rate is highest in infants but there are no data on the subsequent risk of contralateral hernia development purely in this population. This was a study of the incidence of contralateral inguinal hernia following unilateral inguinal herniotomy in infancy (aged less than 1 year).

Methods: All infants who underwent a unilateral inguinal herniotomy between January 1986 and December 1991 were studied retrospectively.

Results: One hundred and eighty-one infants (165 boys and 16 girls) were studied. Median gestational age was 37 (range 25–42) weeks and median age at operation was 87 (range 1–365) days. The herniotomy was right sided in 82·9 per cent of infants. Follow-up ranged from 5 to 10 years. A contralateral hernia/hydrocele developed in 14 infants (7·7 per cent). None of the hernias was incarcerated. Median time from operation to occurrence of the contralateral hernia was 18 (2–67) months. Gestational age, sex and the side of the hernia did not influence the incidence of contralateral hernia development.

Conclusion: The low incidence of contralateral hernia development in infants undergoing a unilateral inguinal herniotomy does not justify routine contralateral groin exploration.

Paper accepted 5 December 2000

British Journal of Surgery 2001, **88**, 720–723

Introduction

Four decades after Rothenberg and Barnett[1] advocated contralateral groin exploration, controversy about the optimal management of a unilateral inguinal hernia in childhood persists. The bilateral approach is advocated on the basis of age[2–6], prematurity[7], incarceration[7], sex[4–6,8] and the side of the hernia[6,9]. A study of the natural history of the processus vaginalis suggests that 40 per cent close at around the time of birth, 20 per cent over the ensuing 2 years and that the patency rate is 40 per cent at the age of 2 years[10]. Morgan and Anson[11] showed that 20 per cent of adult men have a patent processus without a previous history of clinical hernia. Patency of the processus is therefore a poor criterion upon which to base contralateral groin exploration. It would seem more appropriate to be guided by the actual risk of clinical hernia development. Data on long-term risk of contralateral hernia development in children are limited[6–9,12–15] and there are no studies confined exclusively to infancy, when the risk of clinical hernia development is at its highest[16,17]. The aim of this study was to quantify the risk of development of a clinical inguinal hernia in children who had undergone a unilateral inguinal herniotomy in infancy.

Patients and methods

A retrospective study of all patients presenting with a unilateral inguinal hernia between January 1986 and December 1991 was undertaken. Inclusion criteria for the study were age less than 1 year and unilateral inguinal herniotomy. An exclusion criterion was bilateral groin exploration. The case records were reviewed for each patient and the variables evaluated were sex, gestational age, age at operation, initial side of inguinal hernia, development of contralateral hernia, the presence of incarceration, time lapse between initial operation and occurrence of a contralateral hernia, and length of follow-up.

Measures were taken to ensure that patients presenting initially to this institution had not subsequently presented to another hospital in Scotland with a contralateral inguinal hernia. A search was performed by the Information and

Statistics Division of the National Health Service in Scotland, which holds a national database of all admissions and operative procedures.

Results

Some 185 infants presented with a unilateral inguinal hernia over the 6-year period. Four infants were excluded because they underwent repair of a synchronous contralateral hydrocele. One hundred and eighty-one were included in the study. There were 165 boys and 16 girls. Forty-five infants (24·9 per cent) were premature. Median gestational age was 37 (range 25–42) weeks and median age at operation was 87 (range 1–365) days. The initial herniotomy was right sided in 150 infants (82·9 per cent). Follow-up varied from 5 to 10 years.

A contralateral hernia/hydrocele developed in 14 infants (7·7 per cent): 13 boys and one girl. The original herniotomy was right sided in 12 and left sided in two. The findings in the contralateral groin were of a hernia in 12 and a hydrocele in two. None of the metachronous contralateral inguinal hernias presented with incarceration. Data relating to these 14 infants are shown in *Table 1*.

The incidence of a contralateral inguinal hernia was 7·9 per cent in boys and 6 per cent (one of 16) in girls; 6 per cent (two of 31) in left-sided and 8·0 per cent in right-sided hernias; 2 per cent (one of 45) in premature and 9·6 per cent in mature infants.

Table 1 Clinical data relating to patients who presented with a contralateral inguinal hernia

Gestational age (weeks)	40 (28–40)
Age at operation (days)	70 (18–355)
Time from operation to development of contralateral hernia/hydrocele (months)	18 (2–67)

Values are median (range)

Discussion

The published literature on the management of the contralateral groin in children with a unilateral inguinal hernia abounds with conflicting advice. Contralateral groin exploration is not standard practice in the UK. A survey of American surgeons[18] revealed that 65 per cent performed contralateral groin exploration in boys under the age of 2 years and 84 per cent performed the procedure in girls up to the age of 4 years. Impetus for the present study was provided by the lack of long-term data on the risk of contralateral clinical hernia development when herniotomy is performed in infancy.

A contralateral clinical hernia or hydrocele developed in 7·7 per cent of the study population. This low incidence is of the same order of magnitude as that reported in older children (*Table 2*). Therefore, in spite of having a high patency rate of the processus, infants do not have a higher risk of developing a contralateral hernia than older children. This observation is not surprising as it is well documented that there is a high chance of closure of the processus which is open at birth[10] and even those which remain patent do not always manifest as a hernia[11]. The lack of a relationship between the risk of a contralateral hernia and age at operation has also been reported by Given and Rubin[13]. This finding puts into question the practice of exploring the contralateral groin on the basis of early age.

Sex and prematurity, as well as the side of the initial hernia, were not found to influence the incidence of a contralateral hernia. These observations are in agreement with those of Given and Rubin[13] and Kemmotsu *et al.*[14],

Table 2 Published incidence of metachronous contralateral inguinal hernia

Reference	Year	No. of patients	Incidence of metachronous contralateral hernia (%)
Tackett *et al.*[7]	1999	548	8·8
Lym *et al.*[12]	1999	85	7
Kemmotsu *et al.*[14]	1998	1052	11·6
Nazir and Saebo[15]	1996	161	10·6
Ulman *et al.*[6]	1995	245	10·2
Surana and Puri[19]	1993	116	10·3
Given and Rubin[13]	1989	904	5·6
McGregor *et al.*[9]	1980	160	29·0
Bock and Sobye[8]	1970	174	14·9
Santulli and Shaw[20]	1961	359	12·0
Fischer and Mumenthaler[21]	1957	625	11·0
Shidler[22]	1957	57	3
Packard and McLauthlin[23]	1953	681	3·4

who found that sex did not influence the incidence of contralateral hernia development. In contrast, Tackett *et al.*[7] found prematurity to be a predisposing factor. There are conflicting reports of the influence of laterality. Some studies have found a higher incidence of contralateral hernia in infants presenting with a left-sided hernia[6,12] whereas others have not found the side of the hernia to have any effect on contralateral hernia development[13–15]. Pooled data from five series showed that the risk of development of a contralateral hernia was the same irrespective of the side of the presenting hernia[8,9,24].

The follow-up period in this study, which ranged from 5 to 10 years, is considered adequate. Lym *et al.*[12] found that 100 per cent of contralateral hernias had presented by 15 months. Surana and Puri[19] and Given and Rubin[13] reported that 100 per cent had presented by 18 months and over 90 per cent by 5 years respectively.

Based on an incidence of contralateral hernia of 7·7 per cent, 13 contralateral groins would require exploration in order to prevent one hernia. Whether such a practice is justifiable depends partly on the incidence of complications associated with the procedure. Injury to the vas deferens is reported in 1–2 per cent[25,26], decreased testicular size in 2–13 per cent[9,25] and iatrogenic ascent of the testis in 3 per cent of cases[19]. In the light of such data, groin exploration in the absence of a hernia would seem highly questionable.

It is of particular relevance that none of the contralateral hernias in this study population presented with incarceration. None of the clinical reports of contralateral hernia development mention the problem of incarceration. It can therefore be assumed that the risk of a metachronous contralateral hernia presenting with incarceration is minimal.

In conclusion, infants who present with a unilateral inguinal hernia have a low risk of developing a contralateral inguinal hernia. Sex, prematurity and the side of the hernia do not influence the incidence of contralateral hernia development. In an era in which cost-effectiveness and evidence-based practice are gaining wider support, contralateral groin exploration at the time of inguinal herniotomy is hard to justify.

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Original article

Percutaneous endoscopic gastrostomy in patients with ventriculoperitoneal shunts

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Background: Percutaneous endoscopic gastrostomy (PEG) may be required in neurosurgical patients with a persistently depressed neurological status or severe lower cranial nerve palsies. Such patients may have a coexisting hydrocephalus requiring cerebrospinal fluid (CSF) diversion. Despite the risk of infection resulting from exposure to oropharyngeal flora by the pull-through PEG technique and the secondary pneumoperitoneum seen in one-third of patients, simultaneous peritoneal placement of CSF shunt catheters with PEG is the current practice. The aim of the study was to determine the frequency of CSF diversionary procedures in neurosurgical patients undergoing PEG insertion and the occurrence of infective complications in patients with simultaneous placement of a PEG and a ventriculoperitoneal (VP) shunt.

Methods: This was a retrospective review of all neurosurgical patients undergoing PEG. The presence of hydrocephalus, mode of CSF diversion and the development of subsequent infection in those having coexistent distal peritoneal catheter placement and PEG were determined.

Results: PEGs were placed in 42 neurosurgical patients (9·3 per cent of all PEGs inserted), of whom 21 had a coexisting hydrocephalus. Eight of 16 shunts with distal catheter placement in the peritoneal cavity developed infection requiring revision. Infections occurred with greater frequency in patients with a tracheostomy. There were no shunt infections requiring revision in a second group of 21 patients who had a coexisting shunt and tracheostomy without PEG.

Conclusion: Simultaneous placement of a PEG and a VP shunt should be avoided in the acute phase of a patient's hospital admission.

Presented in abstract form to the Autumn Meeting of the Society of British Neurosurgeons, Cork, Ireland, September 1999

Paper accepted 18 January 2001

British Journal of Surgery 2001, **88**, 724–727

Introduction

Percutaneous endoscopic gastrostomy (PEG) was first described in 1980[1]. Its role in long-term enteral nutritional support in patients with an intact gastrointestinal tract but impaired swallowing mechanisms is now well established[2–4]. Neurosurgical patients with a persistently depressed neurological status or severe lower cranial nerve palsies and who require gastrostomy tube feeding may also have a coexisting hydrocephalus requiring a cerebrospinal fluid (CSF) diversionary procedure. Permanent CSF diversion for hydrocephalus usually involves placement of a shunt, such as a ventriculoperitoneal (VP), ventriculopleural or ventriculoatrial shunt. Some 5–10 per cent of all shunts inserted eventually require revision for infection[5–8].

The infective complications of percutaneous gastrostomy include stomal site infection in 2·9–8·8 per cent[9–11] and peritonitis in 0·5–6·6 per cent[10,12–14]. The standard pull-through technique of PEG insertion exposes the gastrostomy tube to oropharyngeal flora. A pneumoperitoneum is also seen after one-third of all PEG insertions. Placement of a PEG is followed by the eventual formation of a mature gastrocutaneous fistula. The exact nature of this tract and the time required to reach maturity is poorly understood. Thus, following PEG there are a number of factors that could lead to an intraperitoneally placed catheter becoming exposed to bacterial pathogens.

Despite the potential additional risk of infection seen with simultaneous placement of the distal catheter of a VP shunt within the peritoneal cavity and a PEG, such coplacement remains the current practice. In fact, an increased rate of VP shunt infection following PEG insertion has not yet been established.

The aims of this study were to determine the proportion of PEGs carried out in neurosurgical patients with coexisting hydrocephalus and the number of infective complications associated with the simultaneous placement of a PEG and a VP shunt.

Patients and methods

All patients undergoing PEG at the Royal Hallamshire Hospital, Sheffield and at Hull Royal Infirmary between November 1995 and April 1999 were reviewed retrospectively, allowing those referred from the Departments of Neurosurgery to be identified. The records of all neurosurgical patients undergoing PEG were examined; variables including the indication for PEG, presence of coexisting hydrocephalus, any CSF diversionary procedure and subsequent development of shunt infection were recorded. Infection was defined as positive CSF/catheter culture or a CSF leucocytosis in association with a non-functioning shunt.

All patients received a commercially available gastrostomy tube introduced by a standard pull-through technique. Procedures were performed under sedation with topical pharyngeal anaesthesia and antibiotic prophylaxis.

Because the indication for PEG in neurosurgical patients is a prolonged depressed level of consciousness or lower cranial nerve palsy, such patients with PEG may also have had a tracheostomy. Records of patients who had a coexistent shunt and tracheostomy without PEG were obtained to ensure that any increased shunt infection could not be accounted for by the presence of a tracheostomy.

Results

Forty-two neurosurgical patients (9·3 per cent of all PEG insertions) were identified (17 females and 25 males of mean age 42·6 (range 14–77) years) with a mean follow-up from PEG insertion of 22·5 (range 7–46) months. Thirty-one neurosurgical patients required PEG feeding for persistently depressed neurological status. Eleven patients required PEG feeding because of severe lower cranial nerve palsies.

Twenty-one neurosurgical patients who required a PEG had coexisting hydrocephalus necessitating CSF diversion. Sixteen permanent CSF diversion procedures involving placement of a distal shunt catheter in the peritoneal cavity were performed on 13 patients. Placement of the shunt occurred in half of these patients before PEG insertion and in half after PEG insertion. The remaining eight patients with hydrocephalus had either temporary external ventricular drainage, or a permanent diversion in the form of a ventriculoatrial shunt, ventriculopleural shunt or endoscopic third ventriculostomy.

Eight of the 16 shunts associated with distal catheter placement in the peritoneal cavity in the presence of a PEG required shunt revision for infection. A further patient with a VP shunt required revision for a peritoneal catheter obstruction. Culture of CSF and the peritoneal catheter end did not yield any organisms. However, omental wrap around of the peritoneal catheter end provoked by colonization of shunt tubing is the most likely cause of the obstruction. This patient was not included in the infected group.

Microbiological analysis of CSF revealed positive cultures in seven episodes; the bacteria cultured were *Staphylococcus epidermidis* (five), *S. aureus* (three) and coliforms (two). One patient, following antibiotic administration, had a CSF leucocytosis with a negative culture.

Shunts with the distal shunt catheter in the peritoneal cavity were divided into two groups: those developing infection (n = 8) and those not developing infection (n = 8). The development of infection was not related to the sequence of, or interval between, shunt and PEG placement. The presence of a tracheostomy during the period of coplacement of the PEG and shunt was noted in all shunts that became infected but in only one that did not become infected.

Twenty-one patients with 22 episodes of a synchronous VP shunt and tracheostomy, without PEG, were also identified. There were no episodes of shunt infection, although one shunt required revision for ventricular catheter obstruction in the absence of CSF leucocytosis or positive cultures. The mean duration of tracheostomy placement was 3 (range 1–12) weeks and the duration of follow-up was similar to that of patients with PEG.

Discussion

In this study, neurosurgical patients accounted for 9·3 per cent of all PEGs inserted. Half of these patients had a coexisting hydrocephalus for which a VP shunt had been performed or was under consideration. A surgeon or endoscopist performing PEGs should therefore have an awareness of the issues concerning PEG insertion in this patient group.

The literature contains only two papers concerned with the coplacement of a PEG with a VP shunt. Graham *et al.*[15] performed a prospective study of adults undergoing PEG a mean of 2·2 weeks following shunt insertion. All patients received periprocedural prophylactic antibiotics. With no shunt infections documented, the authors concluded that a PEG could safely be inserted in patients with VP shunts.

Sane *et al.*[16] retrospectively reviewed 23 children who had a PEG inserted without antibiotic prophylaxis at least 1 month before VP shunt insertion. Two of 23 children demonstrated signs of peritonitis, with subsequent shunt infection. The authors concluded that children with a VP shunt and a PEG are at greater risk of infection, and recommended the use of prophylactic antibiotics at PEG insertion.

Insertion of a PEG should lead to the eventual formation of a mature gastrocutaneous fistula. This process is thought to take several weeks and may be prolonged in patients with impaired wound healing ability, including those with systemic illness or taking steroid medication[17–19]. No patients in this series were on steroid medication. An immature PEG tract may permit bacterial translocation into the peritoneal cavity. Minor peritoneal contamination at the time of PEG insertion may also occur. Either mechanism may lead to infection of an intraperitoneal shunt catheter. Peritoneal contamination may lead initially to shunt colonization rather than infection. Some organisms have the ability to degrade shunt catheter material, forming microscopic colonies within the walls of the catheter which may persist for long periods before the development of clinical features of infection[20,21]. Such colonization may also provoke omental wrapping of the distal catheter tip, leading to shunt obstruction in the absence of overt clinical features of infection. Colonies embedded within the catheter wall may also explain why CSF cultures can be negative despite the presence of an infected shunt device[8,22].

An increased risk of infection with simultaneous placement of a PEG and a VP shunt was associated with the presence of a tracheostomy at the time of coplacement. However, the presence of a tracheostomy without a PEG was not associated with shunt infection. The presence of a tracheostomy, placed during the acute phase of the hospital admission, highlights those patients who are systemically unwell with a potentially reduced host response to minor peritoneal contamination.

In conclusion, neurosurgical patients account for almost 10 per cent of all PEG insertions. Half of these patients have hydrocephalus requiring a permanent CSF diversionary procedure, potentially a VP shunt. Synchronous placement of both a PEG and VP shunt during the acute phase of the hospital admission, when the patient may also have a tracheostomy, results in a 50 per cent shunt infection rate. Tracheostomy alone is not associated with increased shunt infection. Simultaneous placement of a PEG and a VP shunt should be avoided during the acute phase of the hospital admission.

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Correspondence

The Editors welcome topical correspondence from readers relating to articles published in the Journal. Letters should be no more than 250 words in length and should be typed on A4-sized paper in double spacing

Randomized controlled trial of the effect of early enteral nutrition on markers of the inflammatory response in predicted severe acute pancreatitis (*Br J Surg* 2000; 87: 1375-81)

Sir

The authors state, in their inclusion criteria, that all patients suffered severe pancreatitis but the Glasgow scale score was 2 for both groups, with a range of 0–6. In addition APACHE II values were ≥ 7. The Atlanta consensus classified pancreatitis as severe only in those patients with a value > 8. When the Balthazar criteria are applied, most patients would be classified as suffering mild pancreatitis. Fasting time is also short, with a mean of 6 days (range 4–10 days). These data are against the diagnosis of severe pancreatitis. Only seldom does a patient with severe disease begin oral nutrition so quickly. I believe that many of these patients, in fact, suffered mild pancreatitis. In this type of patient, neither enteral nor parenteral nutritional support offers any advantage and, obviously, results do not favour enteral nutrition. Besides, comparing enteral nutrition against conventional management without parenteral nutrition is not methodologically correct if it is accepted that parenteral nutrition is the gold standard as nutritional treatment for patients with severe disease.

Finally, although the authors' intention was to evaluate immune response, a time course of only 4 days does not allow for a real measure of enteral nutrition effects. Moreover, tumour necrosis factor or interleukin-6 measurements have not shown a direct relationship with complication rate. Gianotti *et al.*[1] previously showed that in patients with immunonutrition and cancer at least 10 days of enteral nutrition are necessary to observe an effect of nutritional therapy.

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1 Gianotti L, Braga M, Vignali A, Balzano G, Zerbi A, Bisagni P *et al.* Effect of route of delivery and formulation of postoperative nutritional support in patients undergoing major operations for malignant neoplasms. *Arch Surg* 1997; 132: 1222–30.

Authors' reply

Sir

Dr Sanabria is correct to point out that although all patients had predicted severe acute pancreatitis, 11 (41 per cent) were classified as mild according to Atlanta consensus conference criteria. Clearly, the aim of our trial was to include patients with predicted severe disease and the APACHE II score of 7 was taken as a cut-off expecting a predicted frequency of severe disease in excess of 40 per cent[1].

Dr Sanabria is incorrect, however, to state that from a methodological standpoint, enteral nutrition should have been compared to parenteral nutrition. In the UK, the majority of patients with severe acute pancreatitis do not commence parenteral nutrition on admission but have a variable period of fasting prior to being given nutritional support. Further, a potential methodological flaw inherent in comparing early enteral nutrition to parenteral nutrition is that infectious complications relating to feeding lines may introduce bias.

Finally, the aim of the study was to examine the effect of early enteral nutrition on the early component of the inflammatory response. The demonstration of a lack of effect of treatment may be an indication that the component of the inflammatory process of acute pancreatitis that is driven by a combination of splanchnic hypoperfusion and/or endotoxin translocation may be less relevant in the early stages of the illness.

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1 Johnson CD, Kingsnorth AN, Imrie CW, McMahon MJ, Neoptolemos JP, McKay C *et al* Double blind, randomised, placebo controlled study of a platelet activating factor antagonist, lexipafant, in the treatment and prevention of organ failure in predicted severe acute pancreatitis. *Gut* 2001; 48: 62–9.

Factors predictive of outcome after surgery for faecal incontinence (*Br J Surg* 2000; 87: 1316-30)

Letter 1

Sir

I would like to comment on two pertinent missing points in this review.

Firstly, a number of trials of overlapping sphincter repair were quoted with an average success rate of approximately 75 per cent. It was noted by the authors that the series was heterogeneous with a short follow-up period. A report of the long-term results (55 patients, median follow-up 77 months, minimum 5 years) was published from our unit[1] showing that the initial success rate of 76 per cent[2] fell away drastically with time. After 5 years no patient was fully continent to flatus and less than 10 per cent were fully continent to solid and liquid stool. These disappointing long-term results must be included with the data when considering this operation.

Secondly, no mention of treatment for internal sphincter dysfunction was made throughout the review. There are a number of studies[3–5] that show that injection treatment to augment the internal anal sphincter function has a beneficial effect in patients with intractable passive incontinence who would otherwise be offered a colostomy. Patient selection is based on the finding of a low resting anal sphincter pressure, but a normal or high squeeze pressure, in patients with either intact or isolated defects of the internal anal sphincter on endoanal ultrasonography. The studies report a short-term improvement of continence in 74 per cent of patients.

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Letter 2

Sir

In this extensive description of preoperative assessment and prognostic factors the authors claim that there is no role for magnetic resonance imaging (MRI) because it has a much lower resolution than ultrasonography[1]. This is the case for conventional MRI using a whole-body receiver coil but it has been shown that the use of an endoanal coil enables the detection of anal sphincter defects and external anal sphincter atrophy[2–4]. Conventional endoanal ultrasonography is unable to demonstrate atrophy of the external anal sphincter due to its poor inherent contrast and the sensitive region of the endoanal MRI coil extends beyond the region normally visualized with endoanal ultrasonography. The endoanal MRI finding of external anal sphincter atrophy has been validated histologically[5] and this predicts continence after sphincteroplasty: outcome is significantly better in those without external anal sphincter atrophy[6].

Endoanal MRI is the first imaging technique able to predict functional outcome after sphincter repair. It enables the detection of external sphincter atrophy directly rather than assuming atrophy by detection of pelvic floor denervation by electromyography or pudendal nerve terminal motor latencies. The authors advocate the inclusion of endoanal MRI in the preoperative work-up of patients with faecal incontinence because it helps in deciding on surgical strategy and predicts outcome of surgery in individual patients.

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1 Schafer R, Enck P, Furst G, Kahn T, Frieling T, Lubke HJ. Anatomy of the anal sphincters. Comparison of anal endosonography to magnetic resonance imaging. *Dis Colon Rectum* 1994; **37:** 777–81.
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Author's reply

Sir

I appreciate both points raised by Mr Kenefick. The results of sphincter repair do indeed show significant decline with length of follow-up and size of series. As can be seen by our publications which were cited within the manuscript, our initial success rate[1] declined in subsequent series[2] as was the case at St Mark's Hospital. The issue of treatment for internal sphincter dysfunction is particularly vexing. While the work of Kumar and Shafik are both notable, the technique is yet to gain universal acceptance. Hopefully, additional studies will be forthcoming which will serve to critically assess the benefit of this method.

I also appreciate the comments by Briel *et al.* The role of endoanal magnetic resonance imaging (MRI) is indeed increasing. Unfortunately, the cost and relative unavailability of this technique, as well as the fact that it needs to be performed by radiologists and radiology technicians rather than colorectal surgeons and their assistants, has limited its widespread adoption. If the points raised are confirmed by others, then perhaps their predictions will come to fruition. The fact that endoanal MRI can show sphincter atrophy and that sphincter atrophy, according to them, correlates with poor functional outcome, may be of use. However, the fact remains that like pudendal neuropathy, sphincter atrophy may only be a predictor of outcome rather than a determining factor in selection of the type of therapy. If an anterior external anal sphincter defect is noted, the patient with sphincter atrophy would undoubtedly still undergo an overlapping repair. The atrophy might be used to predict outcome rather than to direct the type of therapy. We certainly hope that Briel *et al.* are correct as the more prognostic information we have preoperatively, the better we can inform patients of realistic expectations.

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1 Wexner SD, Marchetti F, Jagelman DG. The role of sphincteroplasty for fecal incontinence reevaluated: a prospective physiologic and functional review. *Dis Colon Rectum* 1991; **34**: 22-30.
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Causes of re-recurrence after polytetrafluoroethylene patch saphenoplasty for recurrent varicose veins (*Br J Surg* 2000; 87: 1356-60)

Sir

One possible explanation for the claimed advantage of polytetrafluoroethylene patching is the more extensive dissection of the saphenofemoral junction that is required in this procedure. This may lead to a more complete ligation of all the tributaries in this region. Maybe the answer lies in ensuring complete technical success at initial surgery. On-table Doppler studies may provide the answer. Like the authors we agree that more prospective randomized trials are required to determine which surgical technique offers the lowest recurrence rate, if any at all.

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Effect of colectomy on gastric emptying in idiopathic slow-transit constipation (*Br J Surg* 2000; 87: 1193–6)

Sir

I am surprised that this paper was submitted for publication without presenting a prospectively collected, age and sex-matched, control group for comparison. The authors state that the normal range for gastric emptying taken from volunteer studies is 20–76 min. A prospective study from the same department[1], however, showed that the mean(s.d.) gastric emptying time ($t_{1/2}$) in unselected women of similar age was 89(22) min. Most of these controls had an emptying time greater than that which was stated to be the upper limit of normal. This error is understandable when an author tries to harvest some of the data retrospectively. Some of the patients in the present study therefore probably have normal gastric emptying, a fact that has been identified previously[1]. The current publication could be misleading and this might have been avoided if previously published work from the same department had been read thoroughly before being referred to[1].

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1 Macdonald A, Baxter JN, Bessent RG, Gray HW, Finlay IG. Gastric emptying in patients with constipation following childbirth and due to idiopathic slow transit. *Br J Surg* 1997; **84**: 1141–3.

Authors' reply

Sir

While we were aware of Mr Macdonald's publication (our reference 11), we chose to use the normal range accepted by the Department of Nuclear Medicine at Glasgow Royal Infirmary. When corrected for decay of the radionucleide the normal range for gastric emptying is 20–100 min. This corresponds to 20–76 min for uncorrected counts: Mr Macdonald clearly failed to read our text where our use of uncorrected counts is clearly detailed (paragraph four of Patients and Methods). We were surprised at Mr Macdonald's suggestions regarding controls. His entirely female control population would not represent our population of men and women. This, in addition to our use of uncorrected counts, explains the difference between his control group and our quoted normal range. Finally, we doubt whether we would be able to find, as he suggests, an age and sex-matched normal population prepared to undergo colectomy as controls for this study.

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Vascular Reconstructions: Anatomy, Exposures, and Techniques

J. J. Hoballah

285 × 219 mm. Pp. 393. Illustrated 2000 New York Springer. £65·00

There are now several books dealing with the technical aspects of vascular surgery; these are necessary as ordinary textbooks of vascular surgery provide too little detail to be of much help in the operative situation. Previous authors have used various principles and ways of illustrating their points, and their efforts are, to a certain extent, complementary. The obvious question to ask when you see Jamal Hoballah's *Vascular Reconstructions: Anatomy, Exposures, and Techniques* is 'why another one?'. The author has a long experience from workshops in vascular techniques and what is typical of this book is its very detailed, very schematic, step-by-step illustrations (around 900). Alternative technical solutions are brought up. Vascular surgery requires dedication to detail and in this book the detail is dealt with by one illustrator (Sheri Pressler), which I believe is of benefit. The volume seems of value for vascular surgeons in training. What I do not like are the short comments about indications and results. Those belong to textbooks and cannot be left without discussion and analytical commentary. For instance, the table on 4-year patency after infrainguinal reconstructions does not reflect the huge variation in results and the complexity of the problem. Duplex surveillance is also mentioned superficially, and the indications given for inferior mesenteric artery reimplantation could be discussed at length. A book on techniques can stand alone; it does not need supporting text on matters outwith pure technical methodology. Having said this, I like the main parts of this volume where you can learn how to perform vascular surgery in the operating theatre.

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Schein's Common Sense Emergency Abdominal Surgery

M. Schein

235 × 156 mm Pp 382. Illustrated. 2000. Berlin Springer. £30 50

This is a small book on emergency abdominal surgery aimed for 'residents, thinking surgeons and even students'. The book has a soft back and unfortunately is too large to fit in the pocket of a white coat and so cannot be carried around easily. Each chapter starts with a quotation followed by the discussion of topics under subheadings. The first section, 'Before operation', includes a general discussion on the acute abdomen, how to optimize the patient for surgery, the use of preoperative antibiotics, and issues around consent and medicolegal considerations. The second section, 'The operation', has individual chapters on the various conditions that require emergency abdominal surgery. The final section, 'After the operation', covers routine postoperative care and complications including ileus *versus* intestinal obstruction, intra-abdominal abscesses, re-laparotomy and laparostomy for infection, and anastomotic leaks and fistulas.

Most topics are covered adequately, but some of the statements in the book are controversial and would not be accepted practice in the UK. One of the main disadvantages of the book is that it is written in American colloquial language which may be enjoyed by some readers, but is likely to be irritating and tiresome to others. Abbreviations are used that are not standard in UK practice such as LIRS, SIRS, MODS, related to the inflammatory response and sepsis. Tables have been used sparingly, and there are very few figures and no pictures. There are better books on emergency abdominal surgery.

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Scientific Surgery

The *British Journal of Surgery* is committed to practice of surgery based on scientific evidence. Each month we will publish a list of randomized trials and meta-analyses collated from English-language publications. A collection of all these papers will be available in the Scientific Surgery Archive which will be held on the *British Journal of Surgery* website together with links to free Medline sites where the full papers can be accessed (see below for details). If you have published a recent randomized trial which has not been featured in Scientific Surgery, the Editors would be pleased to receive a reprint and consider its inclusion.

Bergh J, Wiklund T, Erikstein B, Lidbrink E, Lindman H, Malmström P *et al.* Tailored fluorouracil, epirubicin, and cyclophosphamide compared with marrow-supported high-dose chemotherapy as adjuvant treatment for high-risk breast cancer: a randomized trial. *Lancet* 2000; **356**: 1384–91.

Two different chemotherapy regimens were tested in 525 women At median follow-up of 34 months, there was a significant increase in relapse rate after conventional over tailored chemotherapy (113 *versus* 81, P=0·04)

Pelzer M, Hartmann B, Blome-Eberwein S, Raff T, Germann G. Effect of recombinant growth hormone on wound healing in severely burned adults. A placebo controlled double-blind phase II study. *Chirurg* 2000; **71**: 1352–8.

Forty-nine badly burned adults (approximately 40 per cent surface area) were included; 37 survived after treatment There was no positive effect on wound or donor site healing rates

Hoibraaten E, Qvigstad E, Arnesen H, Larsen S, Wickstrom E, Sandset PM. Increased risk of recurrent venous thromboembolism during hormone replacement therapy – results of the randomized double-blind, placebo-controlled oestrogen in venous thromboembolism trial (EVTET). *Thromb Haemostas* 2000; **84**: 961–7.

Some 140 women with a history of DVT were randomly allocated HRT or placebo The study was halted prematurely as eight (11 per cent) of the women on HRT had a further DVT compared to only one in the control group

Cafiero F, Gipponi M, Peressini A, Bertoglio S, Lionetto R. Preliminary analysis of a randomized clinical trial of adjuvant postoperative RT *versus* postoperative RT plus 5-FU and levamisole in patients with TNM stage II-III resectable rectal cancer. *J Surg Oncol* 2000; **75**: 80–8.

Some 218 patients were studied. In the chemotherapy group, only 59 per cent completed treatment, there was one chemotherapy-related death and severe toxicity was more common (P=0·03). There was no significant survival advantage from additional chemotherapy

Gupta R, Patel K, Varshney S, Goddard J, Royle GT. A comparison of 5-day and 8-day drainage following mastectomy and axillary clearance. *Eur J Surg Oncol* 2001; **27**: 26–30.

Five-day was as safe as eight-day drainage in this study including 121 patients, but twice as many patients required aspiration of a seroma after short drainage (31 *versus* 16, P=0·03)

Kirton OC, O'Neill PA, Kestner M, Tortella BJ. Perioperative antibiotic use in high-risk penetrating hollow viscus injury: a prospective randomized, double-blind, placebo controlled trial of 24 h *versus* 5 days. *J Trauma* 2000; **49**· 822–32.

There was no significant difference in the number of postoperative surgical site infections in this trial including 317 patients· 10 per cent after 5 days *versus* 8 per cent after 24 h.

Ho Y-H, Cheong W-K, Tsang C, Ho J, Eu K-W, Tang C-L *et al.* Stapled haemorrhoidectomy – cost and effectiveness. Randomized controlled trial including incontinence scoring, anorectal manometry and endoanal ultrasound assessments at up to three months. *Dis Colon Rectum* 2000; **43**: 1666–75.

In this study of 119 operations, postoperative complication rates and hospital stay were similar Stapling reduced the severity of postoperative pain for up to 6 weeks, but was significantly more expensive.

Egger B, Schmid SW, Naef M, Wildi S, Buchler M. Efficacy and safety of weight-adapted Nadroparin calcium *versus* heparin sodium in prevention of clinically evident thromboembolic complications in 1190 general surgical patients. *Dig Surg* 2000; **17**: 602–9.

Two low molecular weight heparin regimens were compared There were no significant differences in the number of bleeding complications or the DVT rate (two after nadroparin *versus* none after heparin).

Ijichi M, Takayama T, Toyoda H, Sano K, Kubota K, Makuuchi M. Randomized trial of the usefulness of a bile leakage test during hepatic resection. *Arch Surg* 2000; **135**: 1395–400.

The bile leakage test was used to identify open hepatic radicles after hepatic resection in 103 patients. Performance of the test and suture of any identified radicles had no effect on the rate of subsequent bile leakage – six per cent after test *versus* four per cent in controls

Shah S, Brooker JC, Williams CB, Thapar C, Saunders BP. Effect of magnetic endoscope imaging on colonoscopy performance: a randomized controlled trial. *Lancet* 2000; **356**: 1718–22.

The two trials included 113 colonoscopies done by trainees and 183 done by a consultant The magnetic endoscope reduced the intubation time and improved the completion rate, particularly for trainees.

The *British Journal of Surgery* website can be found at *www.bjs.co.uk*. In addition to details of current and previous articles featured in Scientific Surgery, the website contains details of the Editorial Team and Board, instructions to prospective authors, links to other sites (such as The Cochrane Library) and forthcoming surgical events. The Editors welcome comments and suggestions about the website, either in writing or through the website address.

Surgical Research Society abstracts

The following abstracts were presented to the 92nd meeting of the Surgical Research Society. The meeting was organized by the Academic Department of Surgery in Cork, Ireland, on 19–20 October 2000. Eighty-eight abstracts were presented during the scientific sessions. The Patey prize was awarded to A. J. Hayes for a paper entitled 'Expression and function of angiopoietin 1 in breast cancer'.

Ischaemic preconditioning protects against systemic inflammation and acute lung injury in lower limb ischaemia–reperfusion

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Background: Ischaemic preconditioning (IPC) of skeletal muscle, by exposure to repeated brief periods of ischaemia–reperfusion (I-R) before a longer ischaemic period, protects against local I-R injury. In a large animal model it was hypothesized that IPC would attenuate the systemic inflammatory response syndrome and acute lung injury associated with limb I-R injury.

Methods: Anaesthetized ventilated swine (six per group) underwent midline laparotomy and were randomized to either: (1) bilateral external iliac artery occlusion (120 min) followed by reperfusion (180 min) (I-R group); (2) IPC (three cycles of 5 min ischaemia, then 5 min reperfusion of both external iliac arteries) followed by I-R (as above) (I-R + IPC group); or (3) laparotomy alone (control group). At the end of the reperfusion period plasma tumour necrosis factor (TNF) α and interleukin (IL) 6 levels were measured as markers of systemic inflammation. Acute lung injury was assessed by arterial–alveolar oxygen (A-a) gradient and lung tissue myeloperoxidase (MPO).

Results:

	Plasma		Lung	
Group	TNF-α (pg ml^{-1})*	IL-6 (pg ml^{-1})*	MPO (units g^{-1})*	A-a gradient†
Control	23·4 (0·6–56·6)	382 (367–568)	7·5 (0·9–8·6)	283·7(70·7)
I-R	76·3 (47·4–106·6)‡	1295 (833–2073)§	33·8 (15·7–52·7)§	476·6(76·8)††
I-R + IPC	8·5 (0·0–33·5)¶	182 (82–417)¶	19·9 (16·8–20·7)**	359·2(43·5)‡‡

Data represent endpoint values ($t = 270$ min): *median (interquartile range) or †mean(s.e.m.). ‡$P < 0·05$, §$P < 0·01$ *versus* control group, ¶$P < 0·01$, **$P < 0·05$ *versus* I-R group (Mann–Whitney *U* test); ††$P < 0·05$ *versus* control group, ‡‡$P < 0·05$ *versus* I-R group (Student's *t* test)

Conclusion: Lower limb I-R induces systemic inflammation and acute lung injury with impaired oxygen transport, associated with lung neutrophil sequestration. IPC prevents the systemic production of TNF-α and IL-6, and attenuates acute lung injury in planned lower limb I-R.

By attenuating the systemic inflammatory response, adenosine pretreatment ameliorates endotoxin-induced multiorgan dysfunction

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Background: Sepsis induces a systemic inflammatory response (SIR) leading to inflammatory-mediated tissue injury and organ dysfunction. It was hypothesized that adenosine would ameliorate endotoxin-induced multiorgan dysfunction by attenuating the SIR.

Methods: With Home Office approval, anaesthetized swine underwent a laparotomy and insertion of a sigmoid tonometer. The control group ($n = 7$) received no further insult. Remaining animals ($n = 14$) received *Escherichia coli* endotoxin (50 µg kg^{-1}) with or without adenosine pretreatment (200 µg kg^{-1} min^{-1}, time (T) = − 60 to + 60 min, then 100 µg kg^{-1} min^{-1}). Blood was taken for blood gas analysis and determination of chemiluminescent phagocyte respiratory burst priming. Interleukin (IL) 1 and IL-6 were assayed by bioassay and enzyme-linked immunosorbent assay respectively. Alveolar–arterial (A-a) gradient (increased with impaired oxygen transport) and sigmoid pH were recorded as markers of organ injury. At $T = 240$ min, bronchoalveolar lavage fluid was obtained and analysed by high-performance liquid chromatography for ascorbate, an antioxidant that is consumed by reaction with free radicals.

Results:

	IL-1 (pg ml^{-1}) $T = 75$	IL-6 (ng ml^{-1}) $T = 240$	Priming (%) $T = 15$	Ascorbate (mmol g protein^{-1})	A-a (mmHg) $T = 270$	Sigmoid pH
Control	44 (26–84)	0·8 (0·7–0·9)	23 (17–41)	16 (6–26)	494 (283–544)	7·34 (7·31–7·36)
LPS	72 (49–87)	230 (124–265)†	51 (42–73)†	11 (5–14)	573 (558–589)†	7·23 (7·19–7·26)†
LPS + adenosine	19 (14–24)*	82 (59–105)*†	28 (18–49)*	28 (12–59)*‡	491 (289–520)	7·34 (7·31–7·37)*

Values are median (interquartile range). *$P < 0·05$ *versus* lipopolysaccharide (LPS), †$P < 0·05$, ‡$P = 0·09$ *versus* control (Mann–Whitney *U* test). T, time in minutes

Conclusion: Endotoxin-induced pulmonary and intestinal injury is associated with a cytokine cascade, phagocyte priming and free radical release. Adenosine pretreatment attenuates this SIR and ameliorates multiorgan dysfunction.

Effect of the nitric oxide–aspirin adduct NCX4016 on neointimal hyperplasia in a model of saphenous vein bypass grafting

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Background: The long-term success of saphenous vein bypass grafting is limited by neointimal hyperplasia (NIH) and no pharmacological intervention has yet proved successful in preventing late vein graft failure in humans. Nitric oxide–aspirin (NO-ASA) adducts consist of aspirin (acetylsalicylic acid) and a nitric oxide-donating moiety. The latter is known to prevent platelet and leucocyte adhesion, to inhibit vascular smooth muscle cells (VSMCs) and to promote vein graft relaxation *in vitro*.
Methods: Bilateral saphenous vein–carotid artery interposition grafting was performed in two groups of Large White pigs (25–31 kg; $n = 6$ per group); the NO-ASA adduct NCX4016 ($60\,\mathrm{mg\,kg^{-1}\,day^{-1}}$) was administered orally to one group and placebo to the control group. After 4 weeks the grafts were explanted and pressure-fixed, and morphometric analysis was performed on representative histological sections by means of computer-aided planimetry.
Results: There was a marked reduction in NIH in animals treated with NCX4016 compared with untreated controls (mean(s.e.m.) neointimal thickness 0·09(0·002 mm) treated *versus* 0·17(0·01) mm control; $P < 0·001$, paired t test). There was no significant difference in medial thickening or luminal area between the two groups.
Conclusion: The NO-ASA adduct NCX4016 significantly reduces neointimal hyperplasia in a porcine model of saphenous vein bypass grafting. This effect, combined with the known antithrombotic properties of aspirin, suggests that this novel drug may have a valuable role in the prevention of both early and late vein graft failure.

Lipopolysaccharide binding protein depletion predicts organ dysfunction following visceral ischaemia–reperfusion in humans

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Background: Lipopolysaccharide binding protein (LBP) is important in the systemic response to endotoxin, and high plasma levels are protective in animal experiments. This study investigated the role of LBP in the development of multiple organ dysfunction (MOD) following visceral ischaemia and reperfusion in humans.
Methods: Arterial blood was collected from 25 consecutive patients undergoing thoracoabdominal aortic aneurysm repair (Crawford stage I, five; stage II, three; stage III, six; stage IV, 11; mean age 64 (range 20–79) years; 18 men, seven women). Levels of LBP and C-reactive protein (CRP), as control, were measured by enzyme-linked immunosorbent assay. Free plasma endotoxin concentration was determined by chromogenic limulus amoebocyte lysate assay. MOD was defined prospectively as failure of two or more organ systems.
Results: Six patients developed organ dysfunction. Their MOD score on day 1 after operation was 19, compared with 10 in patients making an uncomplicated recovery ($P = 0·007$, Mann–Whitney U test). Five patients died.

	LBP ($\mathrm{ng\,ml^{-1}}$)			Endotoxin ($\mathrm{units\,ml^{-1}}$)		
	Preop.	4 h	24 h	Preop.	4 h	24 h
Uncomplicated	7·05(0·76)	6·56(0·53)	15·54(1·0)	1·0(0·4)	8·3(1·4)‡	6·2(1·3)
MOD	6·58(0·87)	3·45(0·67)*	10·93(1·3)†	0·2(0·2)	7·6(4·2)‡	1·5(0·3)

Values are mean(s.e.m.). *$P = 0·006$, †$P = 0·025$ *versus* uncomplicated value (Student's unpaired t test); ‡$P < 0·001$ *versus* preoperative value (paired t test)

CRP did not differ significantly between the two groups at any time point (data not shown).
Conclusion: Significant systemic endotoxin levels were observed, although LBP depletion rather than endotoxin predicted subsequent organ dysfunction. LBP depletion may be therapeutically important during visceral ischaemia–reperfusion in humans.

Probiotic therapy reduces disease activity in patients with ulcerative colitis

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Background: Patients with ulcerative colitis (UC) have a disturbed bacterial flora compared with controls, and several studies have reported a reduction in symptoms by increasing the number of protective colonic bacteria. The effect of *Lactobacillus plantarum* 299 (LP299) on disease activity in patients with UC was investigated.
Methods: Patients recovering from a clinical relapse were randomized into a double-blind controlled trial. Patients drank either 10^{10} colony-forming units of LP299 in an oat fibre (OF) suspension for 3 months or OF alone (control), and were assessed monthly for 6 months. Changes in haematology, biochemistry and Cooke–Prior score were assessed by t tests, and the Mann–Whitney U test was used for clinical outcome, Truelove–Witts category and changes in medication.

Results:

Group	Time period	α_1-Glycoprotein (g l^{-1})	ESR (mm h^{-1})	Cooke–Prior score
LP299 + OF	Month 0	0·98(0·1)	17·9(5·4)	0·7(1·6)
Control	Month 0	1·06(0·1)	24·1(5·2)	0·1(1·2)
LP299 + OF	Months 3–6	0·77(0·1)*	8·7(3·5)*	5·2(1·3)*†
Control	Months 3–6	1·17(0·1)	22·6(3·4)	−1·0(1·5)

Values are mean(s.e.m.). ESR, erythrocyte sedimentation rate. *$P < 0·05$ *versus* control (months 3–6); †$P < 0·05$ *versus* LP299 + OF (month 0)

No differences were observed in haematocrit, haemoglobin, albumin and C-reactive protein levels, Truelove–Witts category, clinical outcome or dosage of any maintenance therapy.
Conclusion: LP299 reduces disease activity in patients with UC as indicated by a reduction in an acute-phase protein, ESR and Cooke–Prior scores. This finding suggests that LP299 is useful as maintenance therapy for patients with UC.

Logistic regression model for carotid endarterectomy

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Background: A 30-day stroke or death rate of 3–10 per cent has been reported in patients undergoing carotid endarterectomy (CEA). The aim of this study was to identify the risk factors that influence the outcome and to develop a logistic regression model that can aid in the comparative audit of CEA.
Methods: Some 839 CEAs performed by four vascular surgeons between 1992 and 1999 were analysed. The median age of the population was 69 (range 38–86) years and the male : female ratio was 1 : 6. Multiple logistic regression was used to model the effect of 67 possible risk factors (46 preoperative and 21 operative) on the 30-day stroke or death rate. The model was initially trained on 604 CEAs and further exposed to 235 CEAs to produce the final version. Observed and predicted outcomes for surgeons and two vascular units were compared with this model.
Results: The overall 30-day stroke and death rate was 3·9 per cent (33 of 839). Regression modelling identified heart disease, diabetes and stroke at presentation as significant risk factors.

No. of risk factors	30-day stroke or death rate
0	1·4 (0·9–2·1)
1	3·4 (0·3–9·7)
2	8·3 (3·2–22·6)
3	18·8 (10·2–35·3)

Values in parentheses are confidence intervals

Observed : predicted outcome ratios varied between individual surgeons, from 0·75 to 1·25, and for the two units were 1·06 and 1·16.
Conclusion: Multiple regression models can successfully identify patients at high risk from CEA and aid in the comparative audit of surgeons and vascular units.

BRCA2 gene mutations in a Scottish male breast cancer population

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Background: Male breast cancer is a rare disease that has previously been linked to *BRCA2* gene mutations in some cases. The aims of this study were to construct family pedigrees, to identify mutations in *BRCA2* and to correlate these with clinical data in a series of men with breast cancer treated in south-east Scotland between 1974 and 1998.
Methods: DNA samples were available from 64 patients. Family pedigrees were constructed by an experienced genealogist. The samples were screened for mutations in the *BRCA2* gene by use of polymerase chain reaction, heteroduplex analysis, protein truncation testing and sequencing. Clinical data for the patients were collected from case records.
Results: Germline *BRCA2* mutations were identified in 12 (19 per cent) of the 64 men with breast cancer, six of whom had a family history of female breast cancer. Sixty-two per cent of the men tested carried a polymorphism in exon 2 of *BRCA2*, compared with 45 per cent of controls ($\chi^2 = 4·88$, 1 d.f., $P = 0·027$). There were no statistically significant differences between men carrying the *BRCA2* mutation and those found to be negative for mutations in terms of age at diagnosis, histological type, disease stage at presentation or survival.
Conclusion: The frequency of *BRCA2* mutations in men with breast cancer from south-east Scotland is higher than that reported previously from the UK (7 per cent) or USA (4–14 per cent). This is the first study to demonstrate a significant association between a polymorphism in exon 2 of *BRCA2* and male breast cancer. The exon 2 polymorphism may be in linkage disequilibrium with a mutation in *BRCA2* or it may in some way alter the transcription of the *BRCA2* gene. This is an interesting area that the authors intend to explore further because it may provide more insight into how *BRCA2* is involved with the development of male and female breast cancer.

Exposure to pneumoperitoneum induces tumour invasiveness via upregulation of the urokinase plasminogen activator system

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Background: The urokinase plasminogen activator (uPA) system is implicated in tumour metastasis. Exposure to the carbon dioxide pneumoperitoneum used in laparoscopic surgery can increase postoperative tumour growth. The effects of pneumoperitoneum on the uPA system were examined and correlated to tumour invasiveness.

Methods: Colonic (SW1222) adenocarcinoma cell lines were exposed to an *in vitro* pneumoperitoneum of carbon dioxide or helium at 3 mmHg, or left in normal growth conditions (control). After 4 h exposure the ability of the cells to invade through an 8·0-μm Transwell filter coated with Matrigel^{TM} (Becton Dickinson, Franklin Lakes, NJ, USA) was analysed by colorimetric methane thiosulphonate assay. This ability was correlated to uPA activity as determined by casein zymography and addition of anti-uPA receptor blocking antibody (Ab).

Results:

	Invasion	Invasion + anti-uPA Ab	Zymographic uPA activity
Carbon dioxide	208(0·8)*	123(9·4)†	264(16)*
Helium	162(0·6)*	105(2·6)†	196(11)*

Values are expressed as mean percentage of control. *$P < 0·01$ *versus* control;. †$P < 0·01$ invasion *versus* invasion + anti-uPA Ab (Tukey–Kramer test)

Conclusion: Exposure of colonic adenocarcinoma to either a carbon dioxide or helium pneumoperitoneum causes increase cell invasiveness, which in part seems to be mediated through the uPA system. A clear enhancement of uPA activity is observed and use of a blocking antibody to the uPA receptor reduces observed invasive capacity.

Effects of interferon γ and lipopolysaccharide on an *in vitro* model of enterocyte barrier function

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Background: The mechanisms that modulate the barrier function of the intestine are still largely unknown. This short study investigated the effects of basal exposure to interferon (IFN) γ (a product of the mucosal immune system) and apical exposure to lipopolysaccharide (LPS; a component of most enteric bacteria) in an *in vitro* model of the gut barrier.

Methods: Confluent polarized monolayers of caco-2 enterocytes were exposed to IFN (basal side; 1000 units ml^{-1}) or LPS (apical side; 10 μg ml^{-1}) for 8 days. Six control and six treatment cell systems were used in each case. Monolayer permeability to horseradish peroxidase (HRP; molecular weight 44 kDa) and fluorescent latex microspheres (1·5 μm in diameter) was then measured over 4 h. These microspheres were chosen because they are approximately the same size as enteric bacteria. Transepithelial electrical resistance (TEER) was also measured after each experiment.

Results: Monolayers treated with IFN had a significantly higher permeability to both HRP (median 70·3 *versus* 6·9 ng ml^{-1} h^{-1}; $P < 0·001$, Mann–Whitney *U* test) and fluorescent microspheres ($2·3 \times 10^5$ *versus* 625 h^{-1}; $P < 0·01$). Monolayers treated with LPS showed a significant rise only in HRP permeability (median 37·1 *versus* 69 ng ml^{-1} h^{-1}; $P < 0·001$). Exposure to both LPS and IFN was associated with a significant fall in TEER.

Conclusion: These results suggest that both LPS and IFN can increase mucosal permeability to small molecules such as HRP. IFN is much more effective than LPS at increasing the transport of larger particles such as latex microspheres and may be involved in potentiating the translocation of bacteria across the gut barrier. These findings may be of importance in elucidating the mucosal events that lead to gut barrier failure.

The 'gut–liver' axis does not drive the systemic inflammatory response after administration of *Escherichia coli* endotoxin

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Background: Alterations in intestinal permeability are thought to drive the systemic inflammatory response (SIR), causing progressive organ failure even after the primary insult has resolved. The aim of this study was to test this hypothesis following endotoxin infusion in swine.

	TNF ($pg\,ml^{-1}$) T=75	IL-1β ($pg\,ml^{-1}$) T=240	IL-6 ($ng\,ml^{-1}$) T=240	IL-8 ($pg\,ml^{-1}$) T=150	IL-10 ($pg\,ml^{-1}$) T=75	Priming (%) T=15
Endotoxin						
Systemic	972·2 (610·2–1127·0)*	88·8 (62·5–151·9)	132·0 (84·8–190·0)*	262·3 (180·0–340·4)*	1542·5 (1291·0–1560·0)*	51·0 (42·0–73·0)*
Portal	662·9 (450·3–1228·0)*	83·5 (78·1–206·5)	230·0 (124·3–265·3)*	243·9 (138·4–351·5)*	1441·5 (1240·0–1600·0)*	59·0 (40·0–89·0)*
Hepatic	626·9 (401·8–1098·0)*	111·5 (83·4–116·1)	133·0 (125·3–214·8)*	258·9 (226·7–341·9)*	1549·5 (1315·0–1600·0)*	47·0 (41·0–68·0)*
Control	20·0 (20·0–29·8)	60·8 (43·5–122·2)	0·8 (0·6–0·9)	55·2 (21·6–194·1)	19·9 (13·4–262·6)	32·0 (20·0–39·0)

Values are median (interquartile range). *$P < 0·05$ *versus* control. *T*, time in minutes

Methods: With Home Office approval, anaesthetized swine underwent a laparotomy and insertion of cannulas into the left carotid artery (systemic sample), portal vein and hepatic vein. Animals ($n = 14$) were randomized to receive Hartmann solution with or without *Escherichia coli* endotoxin (50 μg kg^{-1}). Blood from all three compartments was sampled for determination of whole blood chemiluminescent phagocyte respiratory burst priming. Plasma levels of tumour necrosis factor (TNF) α and interleukin (IL) 6 were measured by bioassay. IL-1β, IL-8 and IL-10 were assayed by enzyme-linked immunosorbent assay.

Results: Intercompartmental and intergroup analyses were carried out with Friedman and Mann–Whitney *U* tests respectively. There was no evidence of selective cytokine production or phagocyte activation by the gut or liver.

Conclusion: There is no evidence of the 'gut–liver' axis driving the SIR following endotoxin infusion in swine.

Bacterial wall products attenuate wound healing by direct effects on endothelial cell vascular endothelial growth factor receptors and vascular endothelial growth factor-directed angiogenesis

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Background: Delayed surgical wound healing due to localized or systemic infection is well recognized and, despite much attention, the mechanisms underlying this phenomenon are poorly understood. The effects of lipopolysaccharide (LPS) and bacterial lipoprotein (BLP) on vascular endothelial growth factor (VEGF) receptor expression on endothelial cells (ECs) and subsequent VEGF-directed EC proliferation were investigated in an *in vitro* study of wound healing.

Methods: Human umbilical vein ECs were exposed to LPS or BLP in both normoxia and hypoxia (2·5 per cent oxygen). VEGF receptor expression was assessed by mean channel fluorescence (MCF) on flow cytometry. Proliferation of LPS- and BLP-treated ECs in response to VEGF was measured by the incorporation of bromodeoxyuridine.

Results: LPS and BLP caused a significant downregulation of EC VEGF receptors in both normoxic and hypoxic (not shown) conditions and attenuated VEGF-directed EC proliferation.

	VEGF receptor (MCF)
Control	108(8)
LPS 100 ng	58(4)*
BLP 100 ng	55(8)*

Values are mean(s.e.m.) *$P < 0.01$ *versus* control (analysis of variance)

	Proliferation
Control	96(14)
LPS	112(25)
BLP	105(32)
VEGF	506(17)*
BLP + VEGF	61(5)*
LPS + VEGF	57(8)*

Values are mean(s.e.m.). *$P < 0.01$ *versus* control (analysis of variance)

Of note, LPS and BLP did not affect normal proliferation, apoptosis or viability in control ECs, nor did they induce cell death.

Conclusion: This study has demonstrated that LPS and BLP are capable of downregulating VEGF receptors on ECs and of inhibiting VEGF-mediated proliferation. This is proposed as a putative mechanism by which bacterial infection attenuates the normal angiogenesis that occurs during the proliferative phase of tissue repair, thus delaying surgical wound healing.

Elucidation of signal transduction pathways in bacterial lipoprotein tolerance

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Background: Endotoxin (lipopolysaccharide; LPS) tolerance is characterized by a diminished production of proinflammatory cytokines and the suppression of the signal transduction mediators, p38 kinase, extracellular signal-regulated kinase (ERK) and nuclear factor (NF) κB. The signal transduction pathways involved in tolerance induction by another ubiquitous bacterial wall product, bacterial lipoprotein (BLP), were investigated.

Methods: Murine macrophages were pretreated with BLP or LPS (10 ng ml^{-1}) for 24 h and further stimulated with high doses of LPS, BLP or LPS + BLP (0·1–1 μg ml^{-1}). Tumour necrosis factor (TNF) α, interleukin (IL) 6, p38 kinase and NF-κB were determined by immunosorbent assay, Western immunoblotting and gel shift assay respectively. In some experiments, instead of inducing tolerance, NF-κB, p38 and ERK were inhibited, and TNF-α and IL-6 were assayed as before. Analysis of variance was used for statistical analysis.

Results:

	BLP (1 μg ml^{-1})		LPS (1 μg ml^{-1})		LPS + BLP (1 + 1 μg ml^{-1})	
	TNF-α	IL-6	TNF-α	IL-6	TNF-α	IL-6
No tolerance	7352 (200)	1493 (31·3)	7643 (256)	3669 (41)	9966 (45)	5657 (7)
BLP tolerance	91 (11)*	145 (21)*	147 (14)*	199 (32)*	201 (21)*	256 (27)*
p38 inhibition	368·4 (59)*	127 (4·6)*	1459 (52)*	870·2 (57)*	3286 (126)*	3394 (309)*
ERK inhibition	4385 (756)*	146 (7·7)*	4688 (507)*	278 (37)*	8311 (306)*	553 (32)*
NF-κB inhibition	1579 (56)*	1570 (40)*	1773 (79)*	2107 (42)*	1891 (64)*	2761 (57)*

Values are mean(s.e.m.). *$P < 0.05$ *versus* no tolerance (analysis of variance)

BLP- and LPS-tolerized macrophages resulted in significantly less TNF-α and IL-6 production and attenuated p38 kinase activation. Proinflammatory cytokine production was also reduced after inhibition of the signal transduction mediators.

Conclusion: BLP tolerance occurs through suppression of p38, ERK and NF-κB. Further elucidation of the signal transduction pathways involved in tolerance induction by bacterial wall products may result in the development of more tailored therapies in the treatment and prevention of polymicrobial sepsis.

Bacterial lipoprotein induces endotoxin-independent tolerance to septic shock

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Background: Endotoxin (lipopolysaccharide; LPS) tolerance protects against a lethal LPS challenge but offers no protection against polymicrobial sepsis. The role of bacterial lipoprotein (BLP), another ubiquitous bacterial wall product in tolerance induction, has not been investigated. It was hypothesized that pretreatment with BLP would induce tolerance against its own lethal effects and might also protect against polymicrobial sepsis.

Methods: Male MF-1 mice were randomized into three groups. Groups 1 and 2 received BLP- and LPS-tolerizing doses by intraperitoneal injection (10 mg kg^{-1}) respectively. After induction of tolerance, all mice were challenged with high doses of LPS or BLP (45 mg kg^{-1} intraperitoneally) or a combination of LPS and BLP (30 + 30 mg kg^{-1} intraperitoneally) or *Staphylococcus aureus* and *Salmonella* (respectively 5×10^8 and 5×10^8 colony-forming units (c.f.u.) per kg intravenously). Group 3 received only high doses of the above agents. Mortality was assessed over 72 h. Serum tumour necrosis factor and interleukin 6 levels were also determined. Statistical analysis for animal survival was performed with the log rank test. Analysis of variance was used for cytokine analysis.

Results:

	Mortality rate (%)		
	No pre-treatment (group 3)	BLP pre-treatment (group 1)	LPS pre-treatment (group 2)
LPS (45 mg kg^{-1})			
24 h	80	40*	10*
48 h	80	40*	20*
BLP(45 mg kg^{-1})			
24 h	60	0*	40
48 h	60	0*	70
LPS + BLP (30 + 30 mg kg^{-1})			
24 h	60	0*	20
48 h	80	0*	40
72 h	0	0	70
Salmonella + *S. aureus* (5×10^8 c.f.u. per kg)			
24 h	66	0*	50
48 h	0	0*	60

*$P < 0{\cdot}05$ *versus* no pretreatment (log rank test)

Induction of tolerance to BLP, but not that to LPS, protects against BLP, BLP + LPS lethality, and polymicrobial sepsis. Proinflammatory cytokine production was significantly attenuated in tolerized mice.

Conclusion: Induction of tolerance to BLP protects against the lethal effects of BLP and endotoxin, producing a cross-tolerance that is not observed following the induction of tolerance to endotoxin. Furthermore, this study demonstrates for the first time that tolerance to BLP also protects against polymicrobial sepsis.

Optimization of the local environment to prevent wound infection in clean wound surgery

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Background: Following anxiety, a cold environment and preoperative starvation, patients may have peripheral shutdown which predisposes to wound infection in clean wound surgery by decreasing blood flow and oxygenation.

Methods: In this prospective controlled clinical study, patients undergoing clean surgery (principally breast, hernia and varicose veins) were randomized into three groups. One group received standard care, another was warmed locally by means of the Warm-up® device (Augustine Medical, Eden Prairie, MN, USA) and the third group was warmed systemically with the Bair-Hugger® (Augustine Medical, Eden Prairie, MN, USA). Warming was delivered for 30–60 min immediately before operation. Measurements included local skin and core temperature, capillary flow using laser Doppler flowmetry and transcutaneous oxygen both before and after warming and following surgery. Postoperative evaluations were performed by a blinded observer for 6 weeks using a diary and scoring system.

Results: Three hundred patients were recruited, of whom 111 (37 per cent) had a hernia, 123 (41 per cent) had breast surgery and 66 (22 per cent) had varicose vein surgery. Two hundred and sixty-one patients (87 per cent) were operated on in the day-case unit and 39 (13 per cent) in the main theatre. Ninety-one per cent had starved for 5–14 h before operation. The wound infection rate was 16 per cent (16 of 102) in the standard group, 2 per cent (two of 101) in the Warm-up group and 5 per cent (five of 97) in the group warmed with the Bair-Hugger. In a cohort of 98 patients who had laser Doppler flowmetry, the blood flow in the Warm-up group increased significantly compared with that in the standard group ($P < 0{\cdot}004$, Wilcoxon test), but there was no difference in the Bair-Hugger group ($P < 0{\cdot}42$, Wilcoxon test). This effect may be due to sweating in the latter group. The local temperature significantly increased in both the Warm-up ($P < 0{\cdot}001$) and the Bair-Hugger ($P < 0{\cdot}003$) group.

Conclusion: Warmed patients have significantly higher local blood flow and temperature, and a lower incidence of postoperative wound infection.

Quantification of intragraft expression of granzyme B and perforin in acute renal allograft rejection

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Background: Both granzyme and perforin have been implicated in the T-cell activation that characterizes acute renal allograft rejection, although existing literature on the utility of intragraft expression of these markers in the diagnosis of rejection is conflicting. The aim of this study was to investigate the role of real-time quantitative reverse transcription–polymerase chain reaction (RT-PCR) in determining expression of perforin and granzyme B in allograft biopsies and to investigate their relationship with the current 'gold standard' of histologically confirmed rejection.

Methods: Ultrasonographically guided renal allograft biopsies were obtained in 37 transplant recipients at the time of acute deterioration in renal function. Two cores of tissue were obtained in each case, one for histological assessment (Banff criteria) and one for messenger RNA (mRNA) extraction, reverse transcription to complementary DNA (cDNA) and subjection to quantitative PCR to determine perforin and granzyme expression.

Results: Copy numbers for perforin and granzyme B varied from 0 to 70 000 copies of cDNA per 25 ng mRNA.

	Banff score		
	1 (normal)	3 (borderline)	4 (rejection)
No granzyme or perforin	75	38	24
Granzyme ± perforin	25	62	75
Sensitivity		62	75
Specificity		75	75
Positive predictive value		67	60
Negative predictive value		71	86

Values are percentages

Conclusion: T-cell activation, as evidenced by granzyme B and perforin expression, was evident in the majority of acute rejection episodes and in a high proportion of borderline rejection cases. However, quantification of these markers did not correlate with histologically assessed severity of rejection.

Unsuspected acute rejection is associated with upregulation of transforming growth factor β_1 messenger RNA expression

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Background: Modern immunosuppressive agents have significantly reduced the frequency of clinical acute rejection episodes, but the chronic graft nephropathy rate has remained unaltered, leading to the hypothesis that there is a significant incidence of subclinical rejection stimulating the fibrotic process. The aim of this study was to determine the incidence of clinical and subclinical acute rejection by means of renal biopsy and to analyse transforming growth factor (TGF) β_1 messenger RNA (mRNA) expression in these biopsies using a novel real-time quantitative polymerase chain reaction (PCR) system.

Methods: Clinical acute rejection episodes were confirmed by biopsy and treated appropriately. Protocol renal biopsies were performed at baseline (time of transplant) and at 3, 6 and 12 months' follow-up. Rejection identified in the protocol biopsies was not treated. Following extraction and reverse transcription, TGF-β_1 mRNA expression in the protocol biopsies was quantified with a Lightcycler™ (Idaho Technology, Salt Lake City, UT, USA) real-time PCR system.

Results: At the time of analysis 46 patients had undergone complete follow-up to 12 months. Twenty-three (50 per cent) suffered no acute rejection episodes, 13 (28 per cent) were treated for acute rejection and ten (22 per cent) had subclinical rejection. TGF-β_1 mRNA expression is shown below as $\log_{10}$ copies per microlitre of RNA with values expressed as mean(s.d.).

Rejection	Baseline	3 months	6 months	12 months
None	1·69(1·40)	1·66(1·42)	1·84(1·49)*	2·10(1·35)
Clinical	1·88(0·98)	2·00(1·66)	2·54(1·54)	2·37(1·31)
Subclinical	1·73(0·90)	2·43(0·90)	3·14(1·21)	2·83(1·21)

Values are mean(s.d.). *$P < 0·05$ *versus* subclinical rejection (Student's *t* test)

Conclusion: A high incidence of subclinical rejection was identified; TGF-β_1 expression was found to be greatest in this group. The identification of TGF-β_1 upregulation in early protocol biopsies may present a marker for the subsequent development of chronic graft nephropathy and allow a window for therapeutic intervention.

Comparison of patients randomized to tacrolimus- or cyclosporin-based immunosuppression and the relative roles of attack, defence, repair and regeneration in the post-transplant environment

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Background: The aim of this study was to determine the relative roles of defence, repair and regeneration mechanisms that naturally counterbalance the immune damage seen in allograft rejection, and to compare any differences existing between patients receiving cyclosporin and those prescribed tacrolimus-based immunosuppression.

Methods: Plasma levels of von Willebrand factor (vWF), selenium, transforming growth factor (TGF) β_1 and hepatocyte growth factor (HGF) were determined in 40 primary cadaveric renal transplant recipients receiving calcineurin inhibitor-based immunosuppression (cyclosporin, $n = 40$; tacrolimus, $n = 40$).

Results: Values are presented as medians.

	vWF (% normal)	Selenium (μmol l^{-1})	TGF-β_1 (ng ml^{-1})	HGF (pg ml^{-1})
Feature	Attack	Defence	Repair	Regeneration
Cyclosporin				
Baseline	212	0·73	27·9	1000
3 months	227	0·96*	32·4*	725*
6 months	191	0·91*	34·8*	645*
12 months	197	0·98*	34·8*	670*
Tacrolimus				
Baseline	190	0·63	24·9	1150
3 months	186	0·83*	14·7	440*†
6 months	187	0·85*	32·4	515*†
12 months	168	0·92*	47·9*	500*†

*$P < 0·05$ *versus* baseline, †$P < 0·05$ *versus* cyclosporin

Plasma vWF levels remained raised following transplantation. The antioxidant deficiencies of end-stage renal failure normalized, as did the increased HGF levels. TGF-β_1 production increased slowly over the first transplant year in both groups.

Conclusion: Further studies are ongoing to examine the relative influence of the defence, repair and regeneration mechanisms on both graft function and the development of chronic graft nephropathy.

Dietary fat and cellular growth control mechanisms in prostatic cancer

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Background: Diacyl glycerol, which has a raised concentration in malignant prostatic tissue, is considered to be a tumour promoter acting via the protein kinase C (PKC) signalling pathway, involved in cell proliferation and apoptosis. Whether fatty acids (FAs), which are known to modulate prostatic cancer cell proliferation *in vitro*, have an effect on PKC activity and PKC isoenzyme activity in these cells is unknown. This study examined the effects of FAs on PKC activity and on isoenzyme expression and abundance.

Methods: Prostatic cancer LNCaP cells were grown to confluence and exposed to 100 mmol l^{-1} n-6 linoleic acid (LA), n-3 eicosapentaenoic acid (EPA) or n-9 oleic acid (OA) for 48 h. PKC activity was estimated by means of enzyme-linked immunosorbent assay, and Western blotting was used to determine PKC isoenzyme expression.

Results: An increase in PKC activity was detected with all three FAs: 9·5 per cent with OA ($P = 0·80$), 52·8 per cent with EPA ($P = 0·06$) and 65·7 per cent with LA ($P = 0·04$); only the latter was significant. Of the ten isoforms investigated the PKC-ι isoenzyme was significantly increased by all FAs. OA reduced membrane abundance, indicating inhibition of activity. PKC-χ in membrane was reduced by EPA. PKC-δ abundance in membrane was decreased by EPA, LA and OA ($P < 0·05$); OA also reduced the abundance in cytosol.

Conclusion: The observed increase in PKC activity in cells treated with each of the three FAs may explain how FAs can modulate tumour cell growth. Furthermore, the reduction in PKC-χ and PKC-δ activities by n-3 EPA may explain the potential benefits of this FA in the control of tumour growth. Increased PKC-ι abundance reflects increased total PKC activity. Specific effects of these changes on cell function await further elucidation.

Glutamine withdrawal does not affect the barrier properties of enterocytes *in vitro*

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Background: Glutamine is the main metabolic substrate of the enterocytes, which form an important part of the gastrointestinal barrier and prevent the uptake of harmful bacteria and bacterial products from the gut lumen. This study investigated the importance of glutamine in maintaining the barrier properties of enterocytes in an *in vitro* system.

Methods: Caco-2 enterocytes were seeded into the apical side of a two-chamber Transwell system and were maintained in Dulbecco's modified Eagle's medium supplemented with 2 mmol l^{-1} glutamine. Serial measurements were made of transepithelial electrical resistance (TEER), fluorescein sulphonic acid (FSA) clearance and lactate dehydrogenase (LDH) release. Once a confluent monolayer was established, cells were maintained in medium lacking supplemental glutamine ($n = 6$) and with specific glutamine-free medium ($n = 6$). Monolayer TEER and permeability to FSA were measured after 3 days. Test systems were compared with control systems maintained in glutamine-supplemented medium.

Results: Some 15 days after seeding, a confluent cell monolayer was formed that had high electrical resistance, low permeability to FSA and low LDH release. No significant differences were noted in transepithelial resistance, FSA clearance or morphology between control, unsupplemented and glutamine-free monolayer systems.

Conclusion: Caco-2 enterocytes form a confluent cell monolayer which has high electrical resistance and low permeability to small molecules. This model may be useful for further investigation of factors affecting gut barrier function. Monolayer hyperpermeability was not induced either by withdrawal of normal glutamine supplementation or by the use of glutamine-free medium, suggesting that supplemental glutamine is not essential for maintenance of enterocyte barrier function *in vitro*.

Modulation of leukotriene B$_4$ and myeloperoxidase by fatty acid supplements in patients with ulcerative colitis

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Background: Leukotriene (LT) B$_4$ is a potent chemotactic agent for neutrophils, which produce myeloperoxidase (MPO). It has been shown that dietary n-3 essential fatty acids (EFAs) can result in symptomatic improvement in patients with ulcerative colitis, and this study aimed to determine whether these effects may have been mediated through a decrease in LTB$_4$ and MPO.

Methods: Patients with ulcerative colitis ($n = 30$), receiving standard therapy, were randomized to either dietary supplementation with EFAs (eicosapentaenoic acid 3·2 g daily and docosahexaenoic acid 2·4 g per day) or placebo (sunflower oil) for 6 months. MPO and LTB$_4$ in colonic washouts and in serum and plasma were measured before starting therapy, 3 months later and after 6 months.

Results: Values are median (interquartile range). There was a significant reduction in plasma level of MPO after 6 months in patients taking n-3 EFAs compared with the control group (50 (10–94) *versus* 90 (70–116) pg ml^{-1}; P = 0·04). There was a reduction in MPO in colonic washouts from patients receiving n-3 EFAs compared with the control group (32 (0–656) *versus* 1296 (40–3068) pg ml^{-1}; P = 0·06). There was a reduction in the serum LTB$_4$ levels in the n-3 EFA group, and there was no difference in LTB$_4$ levels in colonic washout.

Conclusion: This reduction in MPO level may play a role in the symptomatic improvement with dietary n-3 EFA observed in patients with ulcerative colitis.

Systemic and portal biochemistry after intestinal ischaemia–reperfusion injury

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Background: Intestinal ischaemia–reperfusion injury (IRI) is associated with multisystem failure, including liver failure. This study characterized changes in systemic and portal blood biochemistry after intestinal IRI.

Methods: This experiment was performed under Home Office licence. Two groups of adult rats ($n = 6$) were anaesthetized. Animals in the intestinal IRI group underwent occlusion of the superior mesenteric artery (SMA) for 90 min. A blood sample was taken from the superior mesenteric vein (SMV), the SMA was deoccluded and a further SMV sample was taken at 100 s of reperfusion. Samples were also taken from the inferior vena cava (IVC) and aorta at 130 and 160 s of reperfusion respectively. Control rats had general anaesthetic (GA) only for 90 min, and SMV, IVC and aortic samples were taken after a further 100, 130 and 160 s respectively. Samples were processed immediately by an i-STAT portable clinical analyser (i-STAT Corporation, Princeton, NJ, USA) and Na$^+$, pH, partial pressures of oxygen and carbon dioxide (PO$_2$, PCO$_2$), and haematocrit were determined.

Results: Sodium concentration did not differ between groups at any site sampled. Only haematocrit differed between IVC and aortic samples (IVC: intestinal IRI 0·43(0·007) *versus* control 0·40(0·006), P = 0·004; aorta: intestinal IRI 0·42(0·007) *versus* control 0·38(0·007), P = 0·006). Results for the SMV samples are shown in the *Table*.

	Control	Before reperfusion	After reperfusion
Haematocrit	0·40(0·01)*	0·43(0·01)	0·46(0·01)*†
pH	7·30(0·02)‡	7·14(0·04)	7·23(0·02)*§
Po$_2$ (kPa)	8·35(0·6)	7·62(0·2)	11·72(0·5)¶**
Pco$_2$ (kPa)	8·47(0·4)	10·8(0·9)	8·89(0·4)*

Values are mean(s.e.m.). *P = 0·02, ‡P = 0·004, **P < 0·0005 *versus* pre-perfusion; †P < 0·0005, §P = 0·03, ¶P = 0·002 *versus* control

Conclusion: Acidic oxygen-rich blood is delivered to the liver after intestinal IRI. Haemoconcentration after intestinal IRI is most marked in the SMV, but also affects the systemic circulation.

Neutrophil-mediated skeletal muscle reperfusion injury is complement independent

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Background: The polymorphonuclear leucocyte (PMN) and complement system have long been known to play pathogenic roles in ischaemia–reperfusion injury. This study examined the relative anti-inflammatory contributions of neutrophil depletion and complement inhibition in moderating skeletal muscle reperfusion injury.

Methods: C57BL/6 mice underwent 2 h of bilateral hindlimb ischaemia and 3 h of reperfusion. Extravasation of ^{125}I-labelled albumin injected before reperfusion was used to assess the hindlimb vascular permeability index (PI). Neutropenia was induced by tail vein injection of adsorbed rabbit antimouse antibody (20 mg kg^{-1}). Total complement inhibition was achieved by tail vein injection of 10 mg kg^{-1} of the recombinant complement antagonist, soluble complement receptor type 1 (sCR1). Animals were maintained in accordance with National Research Council guidelines.

Results: Mean(s.e.m.) PI after subtraction of the sham value ($P<0{\cdot}05$, t test with Bonferroni correction) in neutrophil-immunodepleted mice (mean(s.e.m.) absolute PMN count of 102(37) cells per µl; $n=19$) was 1·40(0·08). This result represented a 42 per cent reduction in PI compared with the untreated group ($n=26$) (2·40(0·11); $P<0{\cdot}05$), indicating the primacy of neutrophils in mediating injury. Similarly, the PI following treatment with sCR1 ($n=19$) was 1·18(0·07). This result represents a 51 per cent reduction compared with the untreated group, confirming the pathogenic role of complement in this setting. PI in neutropenic mice (mean(s.e.m.) absolute PMN count 111(74) cells per µl) treated with sCR1 ($n=20$) was 0·68(0·10), representing a 72 per cent reduction in permeability and significantly better than complement inhibition alone ($P<0{\cdot}05$). This result indicates the presence of neutrophil activity despite the absence of complement activation.

Conclusion: Neutrophils and complement mediate skeletal muscle reperfusion injury in an additive and independent fashion. The development of pharmacological agents that combine antagonism of both PMN and complement activation mechanisms would probably be more effective in moderating the injurious sequelae of ischaemia–reperfusion.

Modulation of neutrophil function in an *in vitro* model of hypertonic resuscitation

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Background: Recent studies have proposed hypertonic (7·5 per cent) saline (HTS) as a resuscitation fluid with immunomodulation properties that limit polymorphonuclear neutrophil (PMN)-mediated organ damage. It was hypothesized that this therapy would reduce PMN bactericidal function and increase apoptosis in the blood, and that these changes could be modulated by the osmoregulator taurine.

Methods: PMNs were isolated from healthy volunteers and incubated in 7·5 per cent HTS (diluted to obtain osmolarity similar to that reported in clinical practice following this therapy), for 1–6 h with or without taurine at 1 mg ml^{-1}. Apoptosis, respiratory burst and cell surface adhesion receptor expression were measured by flow cytometry.

Results:

	Control	HTS 1 : 16	HTS 1 : 16 + taurine
Osmolarity (mOsm)	334	475	450
Apoptosis (%)	8(1·9)	19(5·7)*	10(3·0)†
MCF			
Burst	215(12·7)	139(35·0)	186(35·5)
CD11B	568(95·5)	486(20·0)	346(146·5)*
L-Selectin	52(22·0)	10(0·0)*	45(3·0)†

Values are mean(s.e.m.). *$P<0{\cdot}05$ *versus* control, †$P<0{\cdot}05$ *versus* HTS ($n=3$). MCF, mean channel fluorescence

Conclusion: Increased osmolarity as a result of replacement with HTS significantly upregulates PMN apoptosis and downregulates superoxide generation *in vitro*, an effect that is modulated by taurine, thus conserving bactericidal function. Taurine works in synergy with HTS to downregulate CD11B adhesion receptor expression further, and prevents L-selectin shedding, which may further reduce neutrophil migration and resultant tissue damage.

Effects of inspired oxygen concentration in the management of primary blast lung injury

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Background: Management regimens for primary blast lung injury have developed with little scientific rationale. The effects of supplemental oxygen therapy in this condition are unknown.

Methods: Anaesthetized, spontaneously breathing pigs ($n=12$) were divided into two equal groups and exposed to blast. Group 1 received severe (non-fatal) injury and group 2 were subjected to moderate injury. Blood gas analysis was performed before blast and for up to 1 h postblast. At 1 h all animals received supplemental oxygen with an increasing fraction of inspired oxygen ($F\text{i}O_2$) and were then killed. All work complied with the Animals (Scientific Procedures) Act 1986.

Results: Apnoea was recorded in four of six animals in group 1, but in none of the pigs in group 2. In group 1 the mean(s.e.m.) partial pressure of oxygen ($P\text{a}O_2$) was significantly reduced, from 11·4(1·0) kPa to a postblast value of 4·5(1·0) kPa ($P<0{\cdot}05$), which was maintained until 1 h. In group 2, $P\text{a}O_2$ fell after blast, from 10·2(0·8) to 9·0(1·0) kPa, but this was not statistically significant. In group 1, arterial pH fell from 7·46(0·02) to 7·31(0·08) ($P<0{\cdot}05$), but in group 2 there was no significant alteration. At 1 h, a $F\text{i}O_2$ of 100 per cent was required to cause a significant increase in $P\text{a}O_2$ in group 1, whereas in group 2 an $F\text{i}O_2$ of 40 per cent resulted in a significant rise in $P\text{a}O_2$.

Conclusion: Severity of blast injury is reflected in the degree of hypoxaemia and acidosis. In severe injury, ventilation with an $F\text{i}O_2$ of 100 per cent is necessary to correct the hypoxaemia.

Human fracture haematoma is inherently angiogenic

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Background: It was hypothesized that skeletal injury would induce local and systemic angiogenic responses and that fracture site haematoma would be a reservoir of angiogenic cytokines.

Methods: Fracture haematoma and plasma from patients with skeletal injury were assayed for vascular endothelial growth factor (VEGF). Endothelial cells (ECs) were cultured in these samples and angiogenic parameters of EC proliferation (uridine labelling) and tubule formation (*in vitro* Matrigel™ assay (Becton Dickinson, Franklin Lakes, NJ, USA)) were determined. EC viability was assessed by tetrazolium bioreduction. To determine the angiogenic potential *in vivo*, samples were incorporated in a Matrigel vehicle and inserted into a dorsal pocket in adult male mice. After 21 days the gel was removed and the number of ingrowing new blood vessels counted. Values are mean(s.e.m.); $n = 32$ per group. Analysis of variance was used for statistical analysis; $P < 0{\cdot}05$ was considered significant.

Results: Injury increased the level of circulating VEGF compared with the value in control samples (310(45) *versus* 68(3) pg ml^{-1}; $P < 0{\cdot}05$). Patient plasma significantly enhanced EC proliferation to 148(6) per cent of the control value ($P < 0{\cdot}05$). Tubule formation increased with injury compared with the control (312(15) *versus* 194(7) tubules per gel; $P < 0{\cdot}05$). Fracture haematoma contained significantly more VEGF (5335(1020) pg ml^{-1}; $P < 0{\cdot}05$) than subject plasma, yet paradoxically attenuated angiogenesis *in vitro* (proliferation: 24(2) per cent of control, $P < 0{\cdot}05$; tubule formation: 82(6) *versus* 194(7) tubules per gel, $P < 0{\cdot}05$; viability 71(2) per cent of control, $P < 0{\cdot}05$). This cytotoxicity was potassium dependent at a haematoma concentration in excess of 9 mmol l^{-1}. Fracture haematoma induced angiogenesis *in vivo* (control 68(3) *versus* patient plasma 118(7) tubules per gel ($P < 0{\cdot}05$) and fracture haematoma 217(18) tubules per gel ($P < 0{\cdot}05$)), comparable with recombinant murine VEGF at 1000 pg ml^{-1} (243(21) tubules per gel). Pretreatment with a neutralizing antibody to VEGF resulted in blood vessel formation comparable with that in the control (86(18) tubules per gel).

Conclusion: Isolated skeletal injury induces systemic and fracture site states of VEGF-mediated angiogenesis. Fracture haematoma is a reservoir of angiogenic cytokines. The differences in the *in vitro* and *in vivo* results may explain the phenomenon of haematoma resorption–organization that precedes fracture revascularization.

Angiogenic cytokines modulate bone turnover

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Background: Osteoblast apoptosis characterizes physiological, septic, osteoporotic and periprosthetic bone loss. Vascular endothelial growth factor (VEGF) couples osteogenesis and vascularization during skeletogenesis. Basic fibroblast growth factor (bFGF) and platelet-derived growth factor (PDGF) are other angiogenic cytokines involved in bone formation. It was hypothesized that these angiogenic factors would promote osteoblast survival by delaying osteoblast apoptosis.

Methods: Primary human osteoblasts were examined for VEGF kinase insert domain containing receptor (KDR) expression using a binding assay by flow cytometry. Osteoblasts were incubated for 18 h in anti-fatty acid synthase (Fas) immunoglobulin M (1000 ng ml^{-1}) in the presence or absence of tumour necrosis factor (TNF) α (1–100 ng ml^{-1}). Parallel studies were performed in the presence of VEGF and PDGF (from 10 pg ml^{-1} to 10 ng ml^{-1}) and bFGF (1–100 ng ml^{-1}). Osteoblast apoptosis was determined by measuring hypodiploid DNA fragmentation by means of propidium iodide staining on flow cytometry and confirmed with agarose gel electrophoresis. Data are given as mean(s.e.m.) values from four experiments, each in triplicate, expressed as percentage cell apoptosis. Analysis of variance was employed for statistical analysis; $P < 0{\cdot}05$ was considered significant.

Results: TNF-α (100 ng ml^{-1}) enhanced Fas receptor expression ($P = 0{\cdot}0001$) and significantly increased Fas-mediated apoptosis (spontaneous 25·6 per cent *versus* Fas-induced 65·8 per cent and TNF-α 82·3 per cent; both $P < 0{\cdot}05$) but did not induce apoptosis in the absence of Fas. Primary osteoblasts demonstrated high-affinity binding of VEGF, confirming expression of the KDR ($P = 0{\cdot}0003$). VEGF (1 ng ml^{-1}), bFGF (25 ng ml^{-1}) and PDGF (1 ng ml^{-1}) significantly attenuated both spontaneous (6·4, 7·4 and 13·3 per cent respectively *versus* 25·6 per cent; all $P < 0{\cdot}05$) and Fas–TNF-α-induced (38·6, 49·0 and 51·3 per cent respectively *versus* 82·3 per cent; all $P < 0{\cdot}05$) osteoblast apoptosis. VEGF promoted osteoblast survival by increasing the expression of the antiapoptotic genes *BCl2* and *BaX*.

Conclusion: TNF-α causes osteoblast cell death by enhancing Fas-mediated apoptosis. VEGF, bFGF and PDGF at concentrations that regulate angiogenesis protect from TNF-α- and Fas-mediated apoptosis. VEGF is the most potent of the 'angiogenic' signals conferring osteoblast survival. Thus angiogenic cytokines may modulate physiological and pathological osteoblast turnover.

Cardiac function during conventional pneumoperitoneum *versus* mechanical abdominal wall lift in laparoscopic cholecystectomy

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Background: The aim was to investigate whether using mechanical abdominal wall lift (MAWL) in place of conventional pneumoperitoneum (CPP) would minimize the bradycardia and reduction in cardiac output (CO) that occur during CPP.

Methods: Patient consent and ethical approval for the study were obtained. Forty consecutive patients undergoing elective laparoscopic cholecystectomy were randomized into two evenly matched groups, receiving either CPP or MAWL at 12 and 0–4 mmHg of intra-abdominal pressure respectively. A standardized anaesthetic protocol was followed. Episodes of intraoperative bradycardia (less than 40 beats per min) were corrected with 200 g intravenous glycopyrronium. An oesophageal Doppler machine was used to measure CO before and after lift-up–insufflation (T_0, T_1), at head-up (T_2), subsequently every 20 min for the next 60 min (T_3, T_4, T_5), and before and after lift-down–desufflation (T_6, T_7).

Results: In CPP and MAWL groups, nine of 20 and one of 20 patients respectively developed at least one episode of bradycardia requiring glycopyrronium ($\chi^2 = 6{\cdot}5$ with Yates' correction, $P = 0{\cdot}011$).

	CO (l min⁻¹)	
	CPP	MAWL
T_0	5·4(0·26)	5·8(0·33)
T_1	3·8(0·25) *†	5·6(0·32)
T_2	3·7(0·20) *†	5·1(0·29)
T_3	4·1(0·28) *†	5·5(0·34)
T_4	4·4(0·31)	5·7(0·40)
T_5	4·4(0·34)	5·7(0·31)
T_6	5·4(0·35)	5·5(0·32)
T_7	6·4(0·32)	5·9(0·31)

Values are mean(s.e.m.). *$P < 0{\cdot}01$ *versus* MAWL, †$P < 0{\cdot}01$ *versus* T_0 (independent and paired t tests)

Conclusion: MAWL was associated with fewer episodes of bradycardia and lesser reduction in CO than CPP. This may have implications for patients with poor cardiac reserve.

Improvement in disease-free interval and response rate in patients receiving primary chemotherapy with taxotere for breast cancer

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Background: Primary chemotherapy is commonly used to treat breast cancer. The most efficacious drug regimens utilize anthracyclines, but many patients fail to respond to this treatment. The aim of this study was to determine the efficacy of primary taxotere in patients with breast cancer.

Methods: Patients with breast cancer received four pulses of CVAP (cyclophosphamide, vincristine, doxorubicin, prednisolone) chemotherapy. Clinical response was then assessed. Those with a partial (PR) or complete (CR) clinical response were randomized to receive either four further pulses of CVAP or four pulses of taxotere. All patients whose tumours failed to respond received four further pulses of taxotere. Following this chemotherapeutic regimen, clinical response was assessed and surgery was performed. Pathological response was assessed in the resected breast tissue.

Results: To date, 170 patients have been enrolled into the study; 105 were suitable for randomization. In randomized patients after completion of chemotherapy the clinical PR or CR rate was 67 per cent in the CVAP group and 96 per cent in the taxotere group ($\chi^2 = 12{\cdot}57$, $P < 0{\cdot}001$). Non-randomized patients had a clinical PR or CR of 43 per cent. Pathological response in randomized patients was 43 per cent with CVAP and 78 per cent with CVAP and taxotere ($\chi^2 = 2{\cdot}05$, $P = 0{\cdot}15$); in non-randomized responders it was 42 per cent. In addition, patients receiving taxotere had a significantly increased disease-free interval ($P < 0{\cdot}05$).

Conclusion: Primary treatment with taxotere resulted in substantial and significantly increased response rates and disease-free interval.

Role of hyperbaric oxygen therapy in ischaemic, diabetic, lower-extremity ulcers: a double-blind randomized controlled trial

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Background: Some 14–24 per cent of diabetic patients with ischaemic lower-extremity ulcers will require an amputation. Despite much effort toward the prevention of amputation in the past decade, the incidence of lower-extremity amputation in such patients continues to rise. This study aimed to evaluate the role of hyperbaric oxygen therapy in the management of this group of patients.

Methods: Eighteen diabetic patients with ischaemic, non-healing lower-extremity ulcers were recruited in this double-blind study. Patients were assigned randomly to receive either 100 per cent oxygen (treatment group) or air (control group), at 2·4 atmospheres of absolute pressure for 90 min daily, for a total of 30 treatments. Wound surface areas were measured at baseline and then at 2, 4, 6 and 12 weeks, and 6 months.

Results: At 12 weeks, healing with complete epithelialization was achieved in 13 of 19 ulcers in the treatment group compared with four of 14 ulcers in the control group ($P = 0{\cdot}024$, χ^2 test). The mean(s.d.) decrease of the wound area in the treatment group was 83(36) per cent and that in the control group was 56(39) per cent ($P = 0{\cdot}021$, Mann–Whitney U test). There was no difference in major amputation rate between the two groups.

Conclusion: Hyperbaric oxygen therapy enhanced the healing potential of ischaemic, non-healing, diabetic leg ulcers and may be used as a valuable adjunct to conventional therapy when reconstructive surgery is not possible.

Expression and function of angiopoietin 1 in breast cancer

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Background: Angiopoietin 1 (Ang1) is a recently identified angiogenic factor that, signalling through its receptor Tie-2, induces physiological angiogenesis by promoting vascular branching and organization. As tumour angiogenesis depends upon the local production of angiogenic promoters, the role of

Ang1 in tumour neovascularization was investigated under clinical conditions and in animal models.

Methods: Ang1 expression was analysed by reverse transcriptase–polymerase chain reaction, both in cell lines and in clinical specimens using laser capture microdissection to isolate RNA from breast cancer cells juxtaposed to microvessels that had been immunostained for Tie-2. Ang1 was then overexpressed in a breast cancer cell line (MCF-7) alone and with fibroblast growth factor (FGF) 1, an angiogenic factor that increases the tumorigenicity of MCF-7 cells, and these cells were used in tumorigenicity assays (approved by Georgetown University Animal Care and Use Committee).

Results: Despite expression of Ang1 in many breast cancer cell lines, the gene was expressed in only three of 21 breast cancer specimens, even though its receptor Tie-2 was abundant on tumour microvessels. Overexpression of high concentrations of biologically active Ang1, alone or with FGF-1, did not enhance MCF-7 cell tumorigenicity, but instead caused up to a threefold retardation of tumour growth ($P = 0.003$).

Conclusion: Ang1 serves different roles in physiological and pathological angiogenesis. This finding supports previous studies suggesting that the biology of angiogenesis physiologically and in tumours is distinct, and has implications for antiangiogenic therapies.

Cerebral emboli during hip and knee replacement: the role of venous to arterial shunting

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Background: Intraoperative cerebral emboli in hip and knee replacement may contribute to the fat emboli syndrome. The role of venous to arterial circulation (VAC) shunts, usually due to a patent foramen ovale, was investigated.

Methods: Patients undergoing hip ($n = 20$) and knee ($n = 21$) replacement were investigated before operation by transcranial Doppler ultrasonography (TCD) for middle cerebral microbubble emboli following intravenous injection of an air emulsion; VAC shunts were categorized by size and spontaneity. Continuous TCD monitoring during operation was used to detect intraoperative cerebral emboli.

Results: Cerebral emboli occurred only in patients with VAC shunt ($P = 0.012$, Fisher's exact test). Spontaneous VAC shunting (without cough or Valsalva) predicted emboli with an odds ratio of 28 (95 per cent confidence interval 4–198; $P = 0.007$, logistic regression). Large VAC shunts were also related to intraoperative cerebral emboli, which occurred in 13 of the 15 patients with more than 15 microbubble emboli on VAC shunt testing but only in five of the 19 patients with fewer than 16 microbubbles ($P = 0.001$, Fisher's exact test). The number of emboli was also strongly related to the size of the VAC shunt ($P < 0.01$, Spearman test). More emboli occurred during hip than during knee replacement (odds ratio 5·5). Two patients with large spontaneous VAC shunts had 368 and 192 cerebral emboli and suffered unexplained confusion and pancreatitis.

Conclusion: During joint replacement surgery cerebral emboli occur only in patients with a VAC shunt, particularly when it is spontaneous and large. This may explain postoperative confusion. Embolization will inevitably be generalized and may cause other complications.

Cyclo-oxygenase inhibitors reduce tumour size, metastases and serum vascular endothelial growth factor levels in an experimental model of breast carcinoma

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Background: Cyclo-oxygenase (COX) 2 expression is increased in patients with breast cancer. The effect of COX-2 inhibition on breast cancer growth and metastases is unknown.

Methods: Some 50 000 4T1 mammary carcinoma cells were injected into the left mammary fat pad of 9-week-old female BALB/c mice. On day 12 postinjection mice were randomized into three groups ($n = 6$ per group) and given intraperitoneal injections, on alternate days, of a selective COX-2 inhibitor (COX-2 group), a non-selective COX inhibitor (indomethacin group) or drug vehicle (control). Animals were killed when mean tumour size in the control group was 18·7 mm.

Results:

At harvest	Control	Cox-2	Indomethacin
Tumour size (mm)	18·7(1·5)	11·5(1·3)*	10·7(0·9)*
Tumour weight (g)	2·8(0·4)	0·85(0·2)*	0·65(0·1)*
Presence of pleural effusion	2	0	0
No. pulmonary metastases	17(3·4)	6(3·5)*	4(1·3)*
Serum VEGF (pg ml^{-1})	519·4(215·5)	114·2(23·6)	87·16(18·6)*

VEGF, vascular endothelial growth factor. *$P < 0.05$ *versus* control (analysis of variance and Kruskal–Wallis test for non-parametric data)

Conclusion: These data demonstrate that selective and non-selective COX-2 inhibition significantly reduces growth of the primary tumour and the number of spontaneous metastases in an experimental model of breast cancer. This may be mediated by a reduction in the activity of the potent angiogenic factor VEGF.

Activated neutrophils upregulate T-cell responses in patients with acute pancreatitis

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Background: Delayed neutrophil apoptosis is a characteristic of acute pancreatitis in humans. It is not known whether these activated neutrophils are simply mediators of end-organ damage, or whether they may, in addition, be involved in regulating the inflammatory response.

Methods: Polymorphonuclear neutrophils (PMNs) and peripheral blood mononuclear cells (PBMCs) were isolated from patients with acute necrotizing pancreatitis ($n = 5$) and healthy volunteer control subjects, and co-cultured with anti-CD3 monoclonal antibody, to assess the influence of activated neutrophils on T cells. Microwell cell culture inserts were used to separate neutrophils from PBMCs, while allowing diffusion of cytokines and other factors across the membrane. T-cell proliferation and cytokine production were measured by tritiated thymidine incorporation and immunoassay respectively.

Results:

Group	T-cell proliferation (%)	Interleukin 10 (pg ml^{-1})
Control PBMCs + control PMNs	392·0(28·8)*	249(1)
Control PBMCs + pancreatitis PMNs	460·7(32·7)	1848(28)
Pancreatitis PBMCs + control PMNs	138·9(41·0)*†	1310(10)
Pancreatitis PBMCs + pancreatitis PMNs	359·2(24·4)†	1270(10)

Values are mean(s.e.m.). *†$P < 0·001$ (analysis of variance and Tukey–Kramer test respectively)

Despite a marked reduction in anti-CD3-induced T-cell proliferation in pancreatitis compared with that in controls, there was increased proliferation when PBMCs were cultured in the presence of activated neutrophils from patients with pancreatitis. There was an associated increase in production of the anti-inflammatory cytokine interleukin 10.

Conclusion: These results suggest a functional role for delayed neutrophil apoptosis in regulating the inflammatory response in patients with acute pancreatitis.

Antilipopolysaccharide hyperimmune globulin attenuates portal endotoxaemia but not systemic inflammation in lower limb ischaemia–reperfusion injury

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Background: Lower limb ischaemia–reperfusion (I-R) increases gut permeability to endotoxin (lipopolysaccharide; LPS), a potent proinflammatory agent. The resultant systemic inflammatory response syndrome (SIRS) is associated with acute lung injury. The potential of anti-LPS hyperimmune globulin (immunoglobulin (Ig) G) to modulate SIRS after I-R was explored.

Methods: Anaesthetized, ventilated swine (six per group) were randomized after midline laparotomy: bilateral external iliac artery occlusion (120 min) and reperfusion (180 min) (I-R group); I-R plus anti-LPS IgG 20 mg kg^{-1} given intravenously over 30 min at the start of reperfusion (I-R + anti-LPS group); and laparotomy alone (control group). Postreperfusion plasma endotoxin and interleukin (IL) 6 levels were measured as indices of endotoxaemia and systemic inflammation, and lung injury was assessed by determination of mean pulmonary artery pressure (PAP), arterial–alveolar oxygen (A-a) gradient and lung tissue myeloperoxidase (MPO) concentration.

Results:

	Control	I-R	I-R + anti-LPS
Plasma			
Endotoxin (pg ml^{-1})*	18·9 (8·7–78·7)	100·0 (41·5–130·7)‡	8·5 (1·0–31·3)¶
IL-6 (pg ml^{-1})*	382 (367–568)	1295 (833–2073)§	1261 (660–3574)§
Lung			
MPO (units g^{-1})*	7·5 (0·9–8·6)	33·8 (15·7–52·7)‡	25·7 (15·9–38·6)‡
A-a gradient†	283·7 (70·7)	476·6 (76·8)§	548·9 (11·0)§
PAP (mmHg)†	28(2)	42(5)‡	39(5)‡

Data represent endpoint values ($t = 270$ min): *median (interquartile range) (Mann–Whitney U test) and †mean(s.e.m.) (Student's t test). ‡$P < 0·05$, §$P < 0·01$ *versus* control; ¶$P < 0·01$ *versus* I-R

Conclusion: Lower limb I-R, in a fully resuscitated porcine model, is associated with endotoxaemia, systemic inflammation and acute neutrophil-mediated lung injury. Treatment with anti-LPS IgG decreases endotoxaemia but not IL-6 production or acute lung injury in lower limb I-R.

Recombinant P-selectin glycoprotein ligand–immunoglobulin fusion protein moderates local and remote injuries following lower torso ischaemia

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Background: Because neutrophil–endothelial adhesion is a prerequisite leading to activation and injury, the effects of endothelial selectin blockade with recombinant P-selectin glycoprotein ligand–immunoglobulin fusion protein (rPSGL-Ig), a P- and E-selectin antagonist, in moderating lower torso ischaemia–reperfusion injury were examined.

Methods: C57BL/6 mice underwent 2 h of bilateral hindlimb ischaemia and 3 h of reperfusion. Extravasation of ^{125}I-labelled albumin was used to assess hindlimb and lung vascular permeability index (PI). Lung neutrophil sequestration was assayed by myeloperoxidase (MPO) activity. Mice treated with 1 mg kg^{-1} rPSGL-Ig or 1 mg kg^{-1} m20ek.Fc (negative control

for rPSGL-Ig, which is inactive for selectin binding) were compared with an untreated group. Animals were maintained in accordance with National Research Council guidelines.
Results: Respective muscle and lung PIs after subtraction of the sham value following treatment with rPSGL-Ig were 40 and 99 per cent lower than values in the untreated group, but were not moderated in mice treated with m20ek.Fc. Similarly, muscle and lung PIs in mice treated with rPSGL-Ig 30 min after reperfusion but not before, were 20 and 98 per cent reduced respectively. Lung MPO activity was also moderated after treatment with rPSGL-Ig.

Group	*n*	Muscle PI	Lung PI ($\times 10^{-3}$)	Lung MPO (units g^{-1})
rPSGL-Ig	12	1·41(0·04)*	0·3(0·3)*	662(76)*
m20ek·Fc	9	2·31(0·16)	5·4(0·9)	2460(186)
rPSGL-Ig (30 min)	15	1·80(0·13)*	1·2(0·3)*	866(122)*
No treatment	17	2·34(0·16)	6·8(1·8)	2070(212)

Values are mean(s.e.m.). $^*P < 0{\cdot}05$ (*t* test with Bonferroni correction)

Conclusion: rPSGL-Ig attenuates local and remote lung injury following lower torso ischaemia–reperfusion. Significantly, delayed endothelial selectin blockade can also moderate injury.

Inosine attenuates skeletal muscle reperfusion injury

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Background: The aim of this study was to ascertain whether inosine, a stable metabolite of adenosine, modulates skeletal muscle ischaemia–reperfusion injury.
Methods: Anaesthetized male C57BL/6 mice were randomized to receive an intraperitoneal injection of inosine (100 mg kg^{-1}; $n = 6$) or phosphate-buffered saline (PBS; $n = 6$). Some 30 min later, animals underwent bilateral tourniquet hindlimb ischaemia for 2 h, followed by reperfusion for 3 h. Serum levels of tumour necrosis factor (TNF) α and macrophage inflammatory protein (MIP) 2 were measured before ischaemia and at the end of reperfusion. The lungs and muscle (right gastrocnemius) were harvested at the end of reperfusion. Muscle and lung wet : dry weight ratios were used to estimate tissue oedema. Myeloperoxidase (MPO) tissue levels were determined as an estimate of leucosequestration. Data are presented as mean (s.e.m.). Statistical comparison was performed with one-way analysis of variance; $P < 0{\cdot}05$ was considered significant.
Results: Inosine pretreatment resulted in lower MPO levels in muscle ($P = 0{\cdot}02$) and lung ($P = 0{\cdot}0002$) than PBS pretreatment. Similarly, muscle ($P = 0{\cdot}04$) and lung ($P = 0{\cdot}02$) wet : dry ratios were significantly lower with inosine than PBS pretreatment. Postreperfusion serum TNF-α ($P < 0{\cdot}001$) and MIP-2 ($P < 0{\cdot}05$) levels were significantly increased compared with preischaemia values with PBS pretreatment but not with inosine pretreatment.
Conclusion: These findings demonstrate that pretreatment with inosine attenuates local and systemic proinflammatory responses associated with skeletal muscle reperfusion injury.

Effect of acute exercise and oxygen on the antioxidant defence mechanism and on nitric oxide availability in patients with intermittent claudication

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Background: Patients with stable intermittent claudication are generally encouraged to walk. Walking to the limit of pain represents a minor ischaemia–reperfusion episode, potentially generating excess oxygen free radicals. The aim of this study was to investigate the effect of exercise and oxygen on plasma total nitric oxide and red cell glutathione levels in claudicants.
Methods: Four normal subjects and five patients (claudicants) with peripheral arterial disease exercised to fatigue or to the limit of pain respectively. Venous blood samples were taken before and 1 min after exercise. Claudicants repeated the same test while breathing 100 per cent oxygen at 2·4 atmospheres of pressure.
Results: The mean(s.e.m.) red cell glutathione level was significantly reduced after exercise in claudicants, from 1211(425) to 1069(435) μmol l^{-1} ($P = 0{\cdot}043$, Wilcoxon test), whereas the level increased in normal subjects from 1526(229) to 1727(55) μmol l^{-1} ($P = 0{\cdot}032$, Mann–Whitney *U* test). In contrast, the mean(s.e.m.) plasma total nitric oxide level increased after exercise in claudicants from 337(125) to 431(126) μmol l^{-1}, compared with 222(49) to 309(130) μmol l^{-1} in normal subjects. After exercise while breathing oxygen, a paradoxical increase in mean red cell glutathione concentration (compared with breathing air) was observed in the claudicants group, rising from 1350(552) to 1502(307) μmol l^{-1}.
Conclusion: Exercise to the limit of pain does not compromise nitric oxide availability but results in a significant reduction in the antioxidant defence mechanism. Encouraging claudicants to walk through pain may be harmful. Oxygen administration normalized the glutathione response to exercise in claudicants despite the ischaemic episode, and therefore warrants further research.

Vascular endothelial growth factor enhances venous thrombus recanalization and organization

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Background: Vascular endothelial growth factor (VEGF) is found in naturally resolving venous thrombi and may be involved in their recanalization by endothelial cells. The aim of this study was to test the hypothesis that increasing thrombus VEGF levels may accelerate recanalization and organization.

Methods: Thrombi were induced in the rat inferior vena cava by creating a stenosis. Some 30 min after thrombus induction, 1, 10 or 100 ng recombinant human VEGF was injected directly into the thrombus (six animals per group). Control thrombi were injected with the carrier solution ($n = 6$). Thrombi and surrounding tissue were collected after 1 week, fixed and prepared for paraffin sectioning. Sections were taken at 0·5-mm intervals along the length of the thrombus and stained with Martius scarlet blue. Lumen recanalization and thrombus organization (erythrocyte content) were measured by two blinded observers on digitized sections using image analysis software. The study was approved by the Home Office.

Results: There were no differences in thrombus cross-sectional area between the groups. There was a greater area of lumen recanalization in thrombus treated with 10 ng VEGF compared with the control (mean(s.e.m.) 5492(922) *versus* 2949(381) pixels; $P = 0{\cdot}013$, t test assuming unequal variance). There was no significant difference with 1 ng (2344(640) pixels) and 100 ng (3787(627) pixels) VEGF. There was a significant decrease in the mean(s.e.m.) proportion of thrombus erythrocyte content in thrombi treated with all three concentrations of VEGF (1 ng: 30(1·7) per cent, $P = 0{\cdot}002$; 10 ng: 30(2·0) per cent, $P = 0{\cdot}004$; 100 ng: 28(1·9) per cent, $P = 0{\cdot}0002$) compared with the control (37(1·7) per cent) (all t tests assuming unequal variance).

Conclusion: Injecting VEGF into newly formed venous thrombus enhances its recanalization and organization. VEGF therapy may be of use in established venous thrombosis to reduce long-term complications.

Pravastatin prevents hyperglycaemia-induced human vascular endothelial cell apoptosis

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Background: The role of endothelial cell apoptosis in atherogenesis is well established. Hyperglycaemia has been reported to be toxic *in vitro* for endothelial cells, increasing apoptosis and impairing nitric oxide synthesis. The aim of the study was to investigate the role of pravastatin in the prevention of hyperglycaemia-mediated endothelial cell apoptosis.

Methods: Human umbilical vein endothelial cells (HUVECs) were cultured in control media (no glucose) and in hyperglycaemic medium (30 mmol glucose). In separate experiments, HUVECs in hyperglycaemic medium were cultured in the presence of pravastatin at a concentration of 20 and 10 μmol l^{-1}. Cells were treated for a period of 24 h. Apoptosis and necrosis were quantified using dual staining with propidium iodide and anexin V, and analysed by means of flow cytometry. Nitric oxide concentration was determined with the Greiss reaction.

Results:

	Apoptosis (%)	Necrosis (%)	Nitric oxide (%)
Control	7·4(0·3)	1·4(0·4)	100
Hyperglycaemia	15·4(0·4)*	2·1(0·8)	78·4(0·2)*
Pravastatin (μmol l^{-1})			
20	8·8(0·6)†	3·1(0·6)	96·4(0·8)†
10	9·4(0·8)†	2·8(0·8)	91·4(0·7)†

Values are mean(s.e.m.). $^*P < 0{\cdot}05$ *versus* control, $^†P < 0{\cdot}05$ *versus* hyperglycaemia (analysis of variance, Tukey–Kramer *post hoc* test)

These data indicate a reduction in apoptosis and a partial restoration of nitric oxide production to control levels in the hyperglycaemic groups treated with pravastatin; the 20 μm concentration was the most effective.

Conclusion: This study has provided further evidence that pravastatin has endothelial protective effects independent of its lipid-lowering ability which may benefit the diabetic patient at risk of cardiovascular disease.

Homocysteine induces apoptosis in human vascular endothelium

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Background: Apoptosis and raised homocysteine concentration are independently associated with vascular disease. This study aimed to determine whether homocysteine induces apoptosis in human vascular endothelium.

Methods: Human umbilical vein endothelial cells (HUVECs) were co-incubated with D,L-homocysteine, adenosine and erythro-9-(2-hydroxy-3-nonye) adenine (EHNA) (an inhibitor of adenosine degradation), either alone or in combination, for 4 or 24 h. Apoptosis was measured by flow cytometry after staining with annexin V and propidium iodide.

Results: Homocysteine, adenosine or EHNA alone did not induce apoptosis. Homocysteine in combination with adenosine induced apoptosis, an effect increased by co-incubation with EHNA and maximal at 4 h.

	Apoptosis in HUVECs (%)	
	4 h	24 h
Control	7·6(2·2)	9·7(2·2)
Homocysteine	8·8(2·6)	8·7(3·5)
Adenosine	9·5(4·6)	9·1(3·5)
EHNA	8·4(3·9)	9·8(2·8)
Homocysteine + adenosine	20·1(5·2)*	13·7(3·7)*
Homocysteine + adenosine + EHNA	26·4(8·4)*	23·1(8·4)*

Values are mean(s.d.). Concentrations: homocysteine, 0·5 mmol l^{-1}; adenosine, 0·5 mmol l^{-1}; EHNA, 0·1 mmol l^{-1}. $^*P < 0{\cdot}006$ *versus* control (analysis of variance)

Conclusion: Homocysteine and adenosine in combination induce apoptosis in HUVECs, a process augmented by EHNA. The role of homocysteine-induced endothelial apoptosis in vascular disease needs further study.

Microvascular reflexes are influenced by oxygen in diabetic patients with peripheral arterial disease

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Background: Endotheliopathy and vascular denervation are responsible for the abnormal microvascular reflexes seen in diabetic patients and are of importance in the pathogenesis of complications. The influence of oxygen on two classical reflexes, the vasoconstrictive response to leg dependency (VCD) and the vasodilatory response to thermal stimulation (VDT), were investigated in diabetic patients with peripheral arterial disease.

Methods: Eighteen diabetic and three non-diabetic patients with occlusive arterial disease and five normal subjects were recruited. Laser Doppler flowmetry and transcutaneous oximetry were measured on the forefoot in the supine position and then 3 min after leg dependency at 50°. The second set of measurements was taken in the supine position and then 10 min after the laser Doppler probe was heated to 44°C. The tests were repeated while giving the patients 100 per cent oxygen at 2·4 atmospheres of absolute pressure.

Results: Mean tissue oxygenation was 48 mmHg in diabetic patients, 58 mmHg in non-diabetic patients and 68 mmHg in normal subjects. Mean VDT was 600, 744 and 1426 per cent respectively. In contrast, mean VCD was 15, −31 and 39 per cent. However, after oxygen administration to the patients, the mean tissue oxygenation improved to 496 mmHg in the diabetic group and to 777 mmHg in the non-diabetic group ($P < 0{\cdot}001$, Wilcoxon test). Moreover, the mean VDT response increased to 1425 and 924 per cent respectively ($P = 0{\cdot}003$, Wilcoxon test). Furthermore, the mean VCD responses improved to 35 and 40 per cent ($P = 0{\cdot}010$, Wilcoxon test).

Conclusion: These results show that oxygen administration normalizes the reflex vasoconstriction induced by leg dependency and vasodilatation induced by thermal stimulation in diabetic and non-diabetic patients with arterial disease. This suggests an improvement in the endothelial function in both groups of patients and a possible improvement in autonomic nerve function in the diabetic patients.

Endovascular approach to aneurysm repair protects patients from postoperative systemic immune inflammation

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Background: Endovascular abdominal aortic aneurysm (E-AAA) repair has several potential advantages compared with conventional (C-AAA) repair, including reduced surgical injury and attenuated ischaemia–reperfusion injury. The immunological comparison of these approaches has not been performed. This study focused on T-cell and cytokine response to C-AAA and E-AAA.

Methods: Peripheral venous blood samples of 20 patients (12 having C-AAA and eight E-AAA repair) were examined. T-cell expression of surface markers CD69, CD62L and CD25 *in vivo* and production of interleukin (IL) 2, IL-10 and interferon (IFN) γ before operation and 1 week after surgery was assessed by means of dual-colour immunofluorescence and enzyme-linked immunosorbent assay.

Results: Conventional surgery resulted in increased expression of CD69 and CD25, and increased IL-2 production 1 week after operation, compared with preoperative values. These changes were not detected following E-AAA repair. No difference was seen in CD62L, IFN-γ or IL-10 in either group.

	C-AAA	E-AAA
CD25*		
Preop.	10(1)	3(0)
Postop.	32(2)†	16(4)
CD69*		
Preop.	3(1)	3(1)
Postop.	26(4)†	6(1)
IL-2 (ng ml^{-1})		
Preop.	37(7)	44(15)
Postop.	289(42)†	89(10)

Values are mean(s.e.m.). *Percentage of T cells expressing surface marker. †$P < 0{\cdot}05$ *versus* E-AAA

Conclusion: E-AAA repair results in reduced immunoactivation and avoids the development of a proinflammatory T-cell phenotype after operation, as seen following C-AAA repair. These data are consistent with the hypothesis that E-AAA repair may result in reduced systemic inflammation compared with conventional open repair.

Neutrophil elastase release in endovascular abdominal aortic aneurysm repair

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Background: Endovascular repair of abdominal aortic aneurysm (E-AAA) may reduce the acute-phase response (APR) and avoid the reperfusion-associated sequelae of prolonged aortic cross-clamping seen with open repair (O-AAA). E-AAA repair may be associated with the postimplantation syndrome (PIS: fever and leucocytosis 3–4 days following E-AAA repair), which is of unproven aetiology and significance. This syndrome may be reflected by changes in neutrophil-mediated elastase release.

Methods: Twenty-four patients undergoing O-AAA ($n = 12$) and E-AAA ($n = 12$) repair were studied prospectively. Blood samples were taken at baseline (0 h; last clamp off (O-AAA) or balloon deployment of stent (E-AAA)), and at 4, 24, 72 and 144 h, and were analysed for levels of neutrophil elastase–α_1-antitrypsin (α_1-AT) complex (APR marker), free elastase (elastase damage) and total elastase (neutrophil activity).

Results: From baseline (results given as percentage change), free elastase levels rose and fell quickly in patients having O-AAA repair (4 h: +50 per cent, $P = 0{\cdot}039$; 24 h: +45 per cent, $P = 0{\cdot}001$; 72 h: +35 per cent, $P = 0{\cdot}009$), returning to baseline by 144 h. However, in those having E-AAA repair free elastase concentration increased gradually to a maximum at 144 h (+85 per cent, $P = 0{\cdot}01$). Bound elastase concentration increased up to 24 h (4 h: O-AAA +25 per cent, $P = 0{\cdot}05$; E-AAA +25 per cent, $P = 0{\cdot}009$; 24 h: O-AAA +115 per cent, $P = 0{\cdot}09$; E-AAA +100 per cent, $P = 0{\cdot}05$), decreasing to baseline in patients having E-AAA repair by 72 h, but remaining persistently raised in patients having O-AAA repair at 144 h (+145 per cent, $P = 0{\cdot}001$). There was no difference in total elastase levels between O-AAA and E-AAA groups at any time point.

Conclusion: O-AAA repair is associated with a raised level of elastase–α_1-AT complex, consistent with a greater APR, whereas raised levels of free elastase in the E-AAA group imply less binding due to a reduced APR. The differing APR and resultant mediator profiles in O-AAA *versus* E-AAA repair may explain why PIS is seen in the latter group.

Urinary incontinence and the development of faecal incontinence in later life

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Background: Some 15–30 per cent of patients with urinary incontinence also have symptoms of faecal incontinence. The purpose of this study was to determine whether patients with urinary incontinence alone have evidence of subclinical anorectal dysfunction.

Methods: Thirty women with urinary incontinence had anorectal manometry performed; the findings were compared with those of an age-matched control group ($n = 10$). Urodynamics were performed using a standard technique and patients were stratified based on their results into three groups: stress incontinence ($n = 14$), urge incontinence ($n = 10$) and mixed incontinence ($n = 6$).

Results: The mean(s.d.) age of the incontinent group was 51·5(16·8) (range 22–77) years, and that of the control group was 50·8(18·9) (range 25–77) years. Symptom severity and quality of life assessment were similar between the subtypes of urinary incontinence. There was no significant difference in mean or maximum anal canal resting pressure (stress, 71·5 mmHg; urge, 73·9 mmHg; mixed, 51·6 mmHg; control, 78·1 mmHg) and mean or maximum anal canal squeeze pressure (stress, 64·2 mmHg; urge, 93·6 mmHg; mixed, 76·2 mmHg; control, 90 mmHg) between the groups ($P > 0{\cdot}05$, one-way analysis of variance followed by Dunnett's test).

Conclusion: Preliminary evidence suggests that patients with urinary incontinence do not appear to have any significant subclinical abnormalities in anorectal motor function and are therefore not at increased risk of developing faecal incontinence in later life.

Major surgery drives a systemic proinflammatory T-cell response

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Background: The authors have demonstrated previously that major surgery results in activation of the adaptive immune system. This study investigated the mechanism of T-cell activation and pattern of response to injury.

Methods: Isolated peripheral blood mononuclear cells (PBMCs) and serum samples were obtained from 25 patients before operation, 24 h after operation and 1 week following major upper gastrointestinal surgery. Patients' PBMCs were stimulated with staphylococcal enterotoxin B, and cytokine enzyme-linked immunosorbent assay was performed for interleukin (IL) 2 and IL-10 on the 48-h supernatants. PBMCs from healthy volunteers were incubated with patients' serum alone or with serum in the presence of cytotoxic T lymphocyte-associated antigen (CTLA) 4 chimera, a potent inhibitor of antigen presentation, and CD69 expression on $CD3^+$ T cells was assessed by flow cytometry.

Results: IL-2 production increased significantly 24 h and 1 week after operation ($P < 0{\cdot}05$, Kruskal–Wallis test). There was no change in IL-10 production throughout the study period ($P = 0{\cdot}13$, Kruskal–Wallis test). Postoperative serum activated healthy volunteer T cells; this activation was prevented by CTLA-4 (see *Table*).

	Preop.	24 h postop.	1 week postop.
PBMCs	0·6(0·1)	4·5(1·3)*	5·3(1)*
PBMCs + CTLA-4	1·9(0·5)	1·8(0·4)	1·4(0·3)

Values are mean(s.e.m.) percentage of $CD3^+$ cells expressing CD69 following 24 h incubation with serum. *$P < 0{\cdot}05$ *versus* preoperative serum incubation (analysis of variance)

Conclusion: T-cell activation following major surgery occurs via an antigen presentation mechanism. The postoperative T-cell response is proinflammatory, suggesting a role for the adaptive immune system in the development of postoperative systemic inflammatory response syndrome.

Factors that may influence splenic autotransplantation and regeneration

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Background: Splenectomy, elective or traumatic, leads to a lifelong risk of developing fatal overwhelming postsplenectomy infection. However, even with the well documented ability of the spleen to regenerate and the simplicity of carrying out the procedure, intentional splenic autotransplantation appears not to be a widely undertaken procedure. It was postulated that splenic regeneration would be promoted by angiogenic stimulation.

Methods: Twenty-seven male Sprague–Dawley rats were splenectomized and 50 per cent of the spleen was reimplanted into the greater omentum. Group 1 animals ($n = 9$) received no stimulus; in group 2 ($n = 9$) the implanted spleen was sutured into omentum; and in group 3 ($n = 9$) the implanted spleen was injected with 500 μg human recombinant vascular endothelial growth factor VEGF® (Genentech, San Francisco, CA, USA). The clearance of Howell–Jolly bodies was observed. Each animal was killed at 12 weeks; the retrieved spleen was weighed and examined histologically.

Results: A higher rate of splenic regeneration was seen in group 1 animals ($P = 0.0006$). Histologically the tissue examined from rats in group 1 was architecturally similar to normal functioning spleen, whereas tissue specimens from groups 2 and 3 consisted of less lymphoid tissue and many inflammatory changes. Improved clearance of Howell–Jolly bodies was also demonstrated from peripheral red blood cells of samples from group 1 animals ($P = 0.0009$).

Conclusion: The blood supply to regenerated spleen is not as good as that to normal spleen on a weight to weight basis, and the intention was to demonstrate better rates of splenic regeneration and a better quality of splenic architecture by utilizing two angiogenic factors. In demonstrating the converse, the authors showed excellent splenic regeneration in group 1 animals and therefore believe that, as the procedure of splenic autotransplantation is quite simple and theoretically confers possible benefits, it should be part of common surgical practice until disproved.

Alternative to prophylactic antibiotics to reduce infection in clean wound surgery

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Background: The incidence of wound complications, and infection in particular, after clean surgery is higher than generally considered acceptable. Use of prophylactic antibiotics in this group is also debatable.

Methods: In this prospective controlled clinical study, patients undergoing clean surgery (principally breast, hernia and varicose veins) were randomized into three groups. One received standard care, another was locally warmed using the Warm-up® device (Augustine Medical, Eden Prairie, MN, USA) and the third group was warmed systemically with the Bair-Hugger® (Augustine Medical, Eden Prairie, MN, USA). Warming was delivered for 30–60 min immediately after operation. Measurements included local skin and core temperature, capillary flow using laser Doppler flowmetry and transcutaneous oxygen both before and after warming and following surgery. Postoperative evaluations were performed by a blinded observer using a diary and scoring system.

Results: Three hundred patients have been recruited, of mean age 50 years and body mass index 25. There were 171 women (57 per cent). Some 261 patients (87 per cent) were operated on in the day-case unit and 39 (13 per cent) in the main theatre. Wound complications were as follows: nine (3 per cent) developed a wound haematoma (five in the standard group, three in the Warm-up group and one in the Bair-Hugger group). There were seven seromas in the standard group, six in Warm-up group and three in the Bair-Hugger. Wound infection was diagnosed in 16 (16 per cent) of 102 in the standard group, two (2 per cent) of 101 in the Warm-up group and five (5 per cent) of 97 in the systemically warmed group ($P < 0.001$ and $P < 0.019$ respectively, χ^2 test). Most complications were wound abscesses. Four patients receiving prophylactic antibiotics developed wound infection and 16 in the group not given prophylaxis had infection ($P = 0.72$, χ^2 test).

Conclusion: Warming significantly reduces the risk of wound infection, and prophylactic antibiotics appear to make no significant difference. Warming may be an alternative to antibiotic prophylaxis.

Phosphodiesterase inhibitors mediate relaxation of human internal anal sphincter *in vitro*: a possible therapy for the treatment of anal fissure

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Background: The second messengers, cyclic adenosine 5′-monophosphate (cAMP) and cyclic guanosine 5′-monophosphate (cGMP), play central roles in a range of signal transduction pathways, including smooth muscle relaxation. Their levels are tightly regulated both in terms of production, by adenylyl and guanylyl cyclase respectively, and of hydrolysis by phosphodiesterases (PDEs). Eleven families of PDE have been identified and specific inhibitors might provide a novel means of overcoming the spasm of the internal anal sphincter (IAS) associated with anal fissure.

Methods: IAS tissue was obtained from three patients (two men; age range 45–56 years) undergoing proctectomy or abdominoperineal excision of the rectum. Strips of distal IAS were cut with the aid of a dissecting microscope, mounted in a superfusion organ bath under 1 g of tension and superfused continuously with Krebs' solution at 37°C. Cumulative dose–response curves were constructed for each inhibitor in turn by the addition of increasing concentrations in the superfusate. Changes in tone were recorded relative to Krebs' solution containing no calcium.

Results:

	Selective for PDE type	Maximum reduction in tone (%)*	IC_{50} ($\mu mol\,l^{-1}$)
Vinpocentine	1	44·1(8·2)	4·9
EHNA hydrochloride	2	46·9(5·8)	25
Trequinsin	3	56·9(14·3)	0·0013
Rolipram	4	59·4(6·3)	7·8
Zaprinast	5, 6, 9	73·9(4·4)	0·64
Dipyridamole	5, 6, 8, 10, 11	76·1(6·6)	5·2

*Values are mean(s.e.m.). EHNA, erythro-9-((2-hydroxy-3-nonyl)adenine. IC_{50}, 50 per cent inhibitory concentration

Conclusion: The PDE inhibitors are a potential new class of therapeutic agent for the treatment of anal fissure. Further work is necessary to establish tissue and subcellular expression of the PDE subtypes in the different muscle groups of the anal sphincter complex to allow targeted pharmacological manipulation.

Development of a valid and reliable instrument for objective assessment of appropriateness of surgical bed occupancy

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Background: The recent national beds enquiry found subjective evidence of significant inappropriate use of acute hospital beds. The aim of this study was to develop a research tool for objective assessment of appropriateness of surgical bed occupancy.

Methods: Twenty-four objective criteria related to patient condition, surgical intervention and nursing care were incorporated into an instrument. If any one of the criteria was met, the patient's stay was judged appropriate; if none was met, the stay was judged inappropriate. The instrument was modified after initial testing on 40 patients. The reliability and validity of the instrument were then studied on 100 randomly selected patients (median age 70 (interquartile range 55–81) years) on a general surgical unit over a 3-month period. Two research fellows used the instrument separately on the same day to assess each patient's appropriateness of stay. Inter-assessor reliability of the instrument was measured by the extent of agreement between the research fellows. A committee of three consultant surgeons blind to the criteria assessed the patients on the same day as the two researchers. The consultants made a collective decision on each patient's appropriateness of stay based on clinical judgement. The degree of agreement between the consultants' decision ('gold standard') and the instrument was used as a measure of validity of the instrument.

Results: The instrument had 89 per cent ($\kappa = 0{\cdot}75$) inter-assessor reliability and 88 per cent ($\kappa = 0{\cdot}69$) validity. It rated inappropriate bed occupancy as 31 (31 per cent) of 100.

Conclusion: The authors have developed a valid and reliable tool for objective assessment of appropriateness of surgical bed occupancy.

Reoperation rates after 20 752 inguinal herniorrhaphies

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Background: In large-scale descriptive studies, 10–20 per cent of all hernia repairs are for recurrence. Available evidence regarding type of repair *versus* recurrence rates are from hernia specialist centres or from surgeons with a special interest in hernia surgery, and nationwide data on recurrence rates and treatment strategies are not available.

Methods: Prospective recording was undertaken of inguinal/femoral herniorrhaphies in the national Danish Hernia Data Base, in a population of 5 million inhabitants, using reoperation rates as a proxy for recurrence.

Results:

	2-year reoperation rate (%)	
	Primary repair	Repair of recurrence
Sutured posterior wall repair	2·1 (1·7–2·7)	6·3 (4·4–8·7)
Anterior mesh repair	1·1 (0·9–1·3)	3·2 (2·5–4·0)
Laparoscopic repair	1·4 (0·5–3·0)	2·4 (1·3–4·2)

Values in parentheses are 95 per cent confidence intervals

Conclusion: Nationwide epidemiological data from more than 20 000 herniorraphies show a lower rate of reoperation after mesh repair, compared with conventional sutured repair ($P < 0{\cdot}05$).

A P-POSSUM type risk model that includes non-operative patients

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Background: It is becoming unacceptable to practise surgery without the collection of outcome data. However, the non-operative surgical patient is often forgotten in this process.

Methods: POSSUM (Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity) data were collected on 35 110 general surgery admissions over 5·5 years, of which 10 255 patients (29 per cent) underwent no operation but accounted for 35 per cent of the deaths. The data were subjected to P-POSSUM analysis. As this requires operative risk factors, the non-operative patients could not be included. To overcome this, the P-POSSUM methodology was applied to the physiological data alone, producing logistical regression models of outcome (mortality and morbidity).

Results: A risk model based only on physiological data was obtained which successfully predicted mortality in the non-operative patients. Interestingly, this was also successful in predicting mortality in the operative patients. (A similar risk model was successful in predicting morbidity in the operative patients.) Goodness of fit of the models was assessed with the Hosmer–Lemeshow method. This is a null hypothesis test: $P < 0{\cdot}05$ indicates a significant lack of fit, and *vice versa*. Results obtained some 5 years after the data from which the model was formed are typical of the fits obtained: operative patients, $\chi^2 = 7{\cdot}10$, 4 d.f., $P = 0{\cdot}131$; non-operative patients, $\chi^2 = 7{\cdot}05$, 4 d.f., $P = 0{\cdot}13$; all admissions, $\chi^2 = 3{\cdot}15$, 4 d.f., $P = 0{\cdot}53$.

Conclusion: The POSSUM physiological data set alone was shown successfully to model outcomes in non-operative as well as operative patients, and as such could form the basis of a hospital-wide Clinical Minimum Data Set, and perhaps could be used to optimize the choice of time of operation.

Monitoring blood loss with near-infrared spectroscopy

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Background: The decision to transfuse blood is currently based on vague clinical criteria. As blood loss in experimental models relates to increased tissue oxygen extraction on near-infrared spectroscopy (NIRS), NIRS was evaluated as a possible transfusion trigger.

Methods: Regional haemoglobin saturation in the brain ($C\text{SO}_2$; left frontal area) and left calf ($P\text{SO}_2$) was measured with an INVOS® 4100 oximeter (Somanetics, Troy, MN, USA). A Critikon 2001 Cerebral Redox Model (Johnson and Johnson, New Brunswick, NJ, USA) was used to measure total (tHb), oxygenated (O_2Hb) and deoxygenated (HHb) haemoglobin from the right calf in ten blood donors before, during and after blood collection (470 ml). Donor blood volume was calculated from height and weight. Haemoglobin and blood pressure were measured before and after collection. Statistical analysis was by repeated-measures analysis of variance, paired *t* test and linear regression.

Results: Donors lost a mean of 10 (range 8–14) per cent blood volume. Haemoglobin fell from a mean(s.d.) of 140·7(12·7) to 133·6(11·6) g l^{-1} ($P = 0{\cdot}044$) but blood pressure did not change. During collection, $C\text{SO}_2$ and $P\text{SO}_2$ fell by a mean of 1·2 (95 per cent confidence interval (c.i.) – 1 to 3·4) and 2·0 (0·2–3·8) per cent respectively. After collection, the oxygenation index ($\text{HbD} = O_2\text{Hb} - \text{HHb}$) fell by a mean 7·6 (95 per cent c.i. 0·8–14·4), but tHb did not change. There was no recovery by 10 min. Linear regression showed agreement between the fall in $P\text{SO}_2$ after blood collection and volume loss ($r = 0{\cdot}7$, adjusted $R^2 = 0{\cdot}42$, $P = 0{\cdot}025$).

Conclusion: $P\text{SO}_2$ on NIRS relates to blood loss and it may be possible to identify a point of maximal oxygen extraction when blood transfusion is required to prevent tissue hypoxia.

Gastrin gene activation: an early event in the adenoma–carcinoma sequence that may be linked to a mutation in the *APC* gene

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Background: Gastrin is an autocrine growth factor for colorectal adenocarcinomas and is expressed in early colonic adenomas at the gene and protein level. Gastrin promotes carcinogenesis in the APC^{Min} mouse model of familial adenomatous polyposis coli (FAP).

Methods: Gastrin expression was assessed in polyps from patients with FAP and APC^{Min} mice by immunohistochemistry. Temporal gastrin gene expression was measured in the HT29 cell line, with a zinc-inducible *APC* gene, by real-time polymerase chain reaction, using the fluorescent dye, SYBR green. Gastrin neutralization induced by G17 : DT antibodies was evaluated on survival and tumour burden of the APC^{Min} mouse.

Results: Gastrin peptides were expressed in the epithelial cells of polyps from both humans and mice with FAP. HT29 cells autonomously express high levels of gastrin messenger RNA, which were reduced by 70 per cent following induction of the wild-type *APC* gene expression within the cells. G17 : DT antibodies, which neutralize autocrine forms of gastrin, increased the 50 per cent median survival from 84 to 113 days ($P = 0{\cdot}0001$, log rank test) and reduced large intestinal tumour burden by 40 per cent ($P = 0{\cdot}007$, analysis of variance).

Conclusion: *De novo* activation of gastrin within epithelial cells is an early event in the adenoma–carcinoma sequence and may be the result of a mutation in the *APC* gene. Confirmation of its role in colonic carcinogenesis suggests the need for early intervention in high-risk patients.

Identification of the isoform-specific vascular endothelial growth factor receptor, neuropilin 1, and enhanced vascular endothelial growth factor production in colorectal carcinoma

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Background: A novel vascular endothelial growth factor isoform-specific receptor (VEGF_{165}), which is identical to neuropilin (NP) 1, is thought to regulate VEGF-induced angiogenesis. This study was designed to investigate whether the expression of NP-1 in human colorectal carcinoma effected local VEGF production and influenced overall survival.

Methods: Sixty-six paraffin-embedded colorectal tumour biopsies from different patients were subjected to trypsin retrieval and stained with anti-VEGF and anti-NP-1 monoclonal antibodies by standard immunohistochemistry. VEGF staining was analysed at × 400 magnification with a microscope-based image analysis system (CAS 200; Becton Dickinson, Franklin Lakes, NJ, USA) and two investigators graded NP-1 staining as positive or negative. Statistical analysis was performed with the Mann–Whitney *U* test and a Cox proportional hazards model for survival.

Results: Some 35 per cent of tumours stained positive for NP-1. The median percentage positive staining for VEGF was significantly higher in the NP-1$^+$ tumours compared with the NP1$^-$ tumours: 59 *versus* 50 per cent ($P = 0{\cdot}002$). Following multivariate analysis, lymph node status and intratumoral VEGF concentration were both found to be significant prognostic factors for disease recurrence ($P = 0{\cdot}0018$ and $P = 0{\cdot}0292$ respectively) and overall survival ($P = 0{\cdot}0004$ and $P = 0{\cdot}0239$). Sex, age, tumour site, histology and tumour depth were not significant prognostic indicators in multivariate analysis.

Conclusion: This study demonstrates that NP-1 expression in colorectal carcinoma is associated with an overproduction of intratumoral VEGF and a reduced disease-free and overall survival time. It is suggested that NP-1 might therefore be a candidate for targeting by antiangiogenic immunotherapy.

Matched case–control study of adenomatous polyps and *N*-acetyltransferase genotype

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Background: *N*-acetyltransferase (NAT) fast acetylator phenotype expressed by genes *NAT1* and *NAT2* has been associated with colorectal cancer. This study investigated the relationship between NAT, diet and adenomas in a population-based sample of patients attending for flexible sigmoidoscopy screening as part of the FlexiScope Trial.

Methods: Patients with adenomatous polyps (cases) were compared with those with no polyps (controls), matched by sex, age and general practitioner. Subjects were genotyped for *NAT1* and *NAT2* and were assigned fast or slow phenotype according to published guidelines. The effect of *NAT1* and *NAT2* phenotype on risk of developing adenomatous polyps was examined by means of conditional logistic regression on the matched pairs of cases and controls.

Results: Some 332 matched pairs were identified in Leeds; 27 per cent of patients overall were fast acetylators for *NAT1* and 39 per cent for *NAT2*. The phenotypes were not independent, and 51 per cent of patients were fast acetylators at one or other locus.

Fast acetylator	Odds ratio	*P*	No. of pairs
NAT1	1·20 (0·82–1·73)	0·35	310
NAT2	1·40 (1·02–1·92)	0·04	318
NAT1 or *NAT2*	1·48 (1·08–2·02)	0·02	314

Values in parentheses are 95 per cent confidence intervals

A further 624 cases and 683 controls were also available from other areas of the screening programme in Norwich and Portsmouth. The collaborative data showed no evidence of an association with *NAT1* (odds ratio 1·03 (95 per cent confidence interval 0·83–1·28)) or *NAT2* (1·11 (0·92–1·35)).

Conclusion: Both *NAT1* and *NAT2* show activity in the intestine, and these results suggest that fast acetylation from either enzyme may increase the risk of adenoma. The variation in relative risk across centres may be due to differences in exposure to environmental factors such as diet and smoking.

Influence of mismatch repair and *p53* status on genetic aberrations as detected by comparative genomic hybridization

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Background: Previous work has demonstrated that colorectal primary tumours have a very heterogeneous genotype as assessed by comparative genomic hybridization (CGH) with a wide spectrum of recognized and novel aberrations. Defects in the mismatch repair (MMR) genes and alterations in the *p53* tumour suppressor gene are known to contribute to different phenotypes of colorectal carcinogenesis; however, their impact on genotype remains undefined.

Methods: CGH was performed on tumour DNA samples and immunohistochemical analysis was used to determine expression of the MMR genes *hMLH1* and *hMSH2*, and p53 protein expression on tumour and adjacent normal tissue.

Results: Forty-nine tumours were studied with follow-up available over a median (range) of 42 (26–55) months. Tumours demonstrated 4 (0–19) amplifications and 7 (0–15) deletions. p53 was overexpressed in 23 tumours (47 per cent) and was associated with impaired survival ($P = 0{\cdot}045$, log rank test). Six tumours demonstrated MMR deficiency (five *hMLH1*), only one of which came from a proband with hereditary non-polyposis colorectal cancer. All MMR-defective tumours were p53 positive and right sided. p53-positive tumours had more aberrations than p53-negative ones (median (range) 15 (1–36) *versus* 8 (0–30); $P = 0{\cdot}04$, Mann–Whitney *U* test). MMR-defective tumours had only 4 (0–8) aberrations, significantly less than p53-positive ($P = 0{\cdot}003$) and p53-negative/MMR intact tumours. There was no difference in number of aberrations between p53-positive and p53-negative/MMR intact tumours. Amplification at 8q21 was found in seven of 20 p53-negative/MMR intact tumours *versus* 16 of 23 p53-positive tumours (P = 0·023, χ^2 test). Amplification of 12q13-15 was found in nine of 20 *versus* four of 23 tumours respectively (P = 0·048) and amplification of 13q21-22 in eight of 20 *versus* 18 of 23 (P = 0·01).

Conclusion: MMR-defective tumours demonstrate minimal chromosomal aberrations on CGH. Furthermore, tumours that are p53 negative with an intact MMR gene profile have as many aberrations as p53-positive tumours and demonstrate a number of specific chromosomal aberrations worthy of further investigation.

Role of 3q gain in solid tumour formation

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Background: 3q has often been identified as a region of copy number change in solid tumours. The aim of this study was to identify the incidence and clinical significance of 3q gain in a range of solid tumours.

Methods: Sixty-seven breast, 50 colorectal, and 38 head and neck tumours were analysed by comparative genomic hybridization (CGH). CGH is based on the competitive hybridization of two differentially labelled DNA samples to normal metaphase spreads. All tumours were graded according to standard Union Internacional Contra la Cancrum (UICC) criteria. 3q gain was studied in relation to standard prognostic markers by means of Fisher's exact test or the χ^2 test for trend.

Results: 3q gain was identified in 18 (27 per cent) of 67 breast tumours, and correlated with grade (P = 0·0061) and Nottingham Prognostic Index (P = 0·0062). A subset of 40 breast tumours was analysed for telomerase activity using the Telomeric Repeat Amplification Protocol (TRAP assay; Boehringer Mannheim, Mannheim, Germany). 3q gain was found to correlate with tumours with high-level telomerase expression (P = 0·019). In head and neck tumours 3q was the most common gain identified, occurring in 61 per cent (23 of 38) of the tumours. The gain did not, however, correlate with any prognostic markers. In the colorectal tumours 3q gain was identified in 22 per cent of tumours (11 of 50), and was not found to correlate with any prognostic markers. In each tumour type the 3q gain encompassed the 3q23-26 loci; to date, no oncogenes have been reported at this region.

Conclusion: These results confirm the importance of 3q gain in solid tumours, identifying the 3q23-26 loci as the region of interest. The 3q gain occurred at a similar frequency in breast and colorectal tumours, and at a higher frequency in head and neck tumours, although clinical significance was identified only in breast tumours, indicating that the role of 3q gain is different between tumour types.

Phase I study of photodynamic therapy using temoporfin in patients with advanced colorectal cancer

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Background: Photodynamic therapy (PDT) uses visible light and a tumour-localizing photosensitizer to destroy cancer tissue. Temoporfin is a new and possibly more effective photosensitizer. Its safety and efficacy for PDT were assessed in patients with advanced colorectal cancer.

Methods: Seven treatments were given to men of mean age 56·4 (range 46–72) years with recurrent advanced colorectal carcinoma. Temoporfin 0·15 mg kg^{-1} was administered intravenously followed by subsequent light delivery at 652 nm from a diode laser. Direct interstitial PDT (IPDT) to ten liver metastases from a cylindrical 2-cm light diffuser at doses of 50–100 J cm^{-2} was performed. One patient received adjuvant intraoperative PDT to a tumour bed.

Results: Following PDT the 30-day mortality rate was zero. Two patients suffered hepatic pain after IPDT from perihepatic bleeding from the optical fibre puncture sites. No skin photosensitivity occurred. Seven hepatic metastases after three PDT treatments were evaluated with computed tomography before and after IPDT. Following IPDT, negative and static growth was observed in three metastases. The mean diameter of liver metastases (n = 7) after IPDT was 4·79 (range from ~3 to 6·6) arbitrary units, and was reduced compared with values before treatment (7·05 (3·5–11·0) arbitrary units), although the difference was not statistically significant (paired t test).

Conclusion: This study demonstrates that PDT using temoporfin can be administered safely with no skin photosensitivity reactions. Treatment complications do occur but are related to the surgical aspect of the treatment. Biological efficacy is confirmed by reduced growth of hepatic colorectal metastases.

Molecular basis of aspirin-induced apoptosis in colorectal cancer

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Background: Aspirin appears to protect against colorectal cancer (CRC) and so elucidation of the molecular basis of the effect will inform the design of novel chemoprevention agents. As nuclear factor (NF) κB regulates the transcription of several cellular proliferation and apoptosis genes, and deranged NF-κB signalling has also been observed in cancer, the hypothesis that aspirin induces apoptosis by modulating NF-κB signalling was tested.

Methods: CRC cell lines (n = 8, including an HRT18 clone expressing mutant I-κB which resists degradation, thereby preventing nuclear entry and activation of NF-κB) and non-colonic cell lines (n = 6) were treated with aspirin 0–10 mmol l^{-1} for 24 h. Cells were counted and the apoptotic fraction was assessed with annexin V and acridine orange. Cytoplasmic and nuclear protein extracts were analysed by Western blotting for I-κB levels and gel-shift assays for nuclear NF-κB. Cytoplasmic I-κB was measured in extracts from rectal cancer biopsies before and after aspirin treatment. Statistical analysis was by paired *t* test and correlation.

Results: Aspirin had no effect in non-colonic lines, but did induce a dose-dependent reduction in the cell viability of all CRC lines ($P < 0{\cdot}05$), paralleled by proportionate increases in apoptosis. Mean 50 per cent lethal concentration in CRC lines was 3·56 (range 2·19–5·3) mmol l^{-1}. Aspirin induced dose-related degradation of I-κB specifically in CRC lines ($P < 0{\cdot}05$), correlating with decreased cell viability ($r = 0{\cdot}9$) and NF-κB nuclear translocation. I-κB degradation, NF-κB nuclear translocation and apoptosis were abrogated in HRT18 cells expressing mutant I-κB, confirming that I-κB degradation is required for aspirin-induced apoptosis. I-κB degradation was also observed after aspirin treatment in rectal cancer biopsies.

Conclusion: Aspirin induces apoptosis specifically in CRC cells by inducing I-κB degradation and NF-κB nuclear translocation. The clinical studies in patients with rectal cancer demonstrate that aspirin modulates NF-κB signalling *in vivo*, thus identifying new targets for research in colorectal cancer chemoprevention.

Upregulation of Fas/FasL (CD95/CD95L)-mediated epithelial apoptosis: a novel therapeutic target in pouchitis

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Background: Pouchitis causes considerable morbidity in 40 per cent of patients with ileal pouch–anal anastomosis. A role was postulated for increased epithelial apoptosis in the aetiology of pouchitis.

Methods: Following ethical approval two groups were recruited. Group 1 ($n = 12$) comprised patients known to have pouchitis, and patients in group 2 ($n = 12$) were pouchitis-free. Cell surface fatty acid synthase ligand (FasL) was detected immunohistochemically. Cytoplasmic caspase activity was detected by means of a monoclonal antibody (M30). Terminal deoxyribonucleotidyl transferase-mediated dUTP (2′-deoxyuridine 5′-triphosphate) nick end labelling (TUNEL) identified DNA fragmentation. Villous atrophy (epithelial surface length/lamina propria surface area) was assessed histologically and correlated with apoptosis. Means were compared with the Wilcoxon rank sum test.

Results: A significant increase in epithelial TUNEL, M30 immunoreactivity and villous atrophy was seen in patients in group 1. Upregulation of FasL was characteristic of this epithelium. Increased epithelial apoptosis correlated with increased villous atrophy.

	Group 1 (pouchitis)	Group 2 (no pouchitis)
TUNEL (apoptotic index)	0·091(0·048)	0·0357(0·007)*
M30 (apoptotic index)	0·225(0·05)	0·082(0·03)*
Villous atrophy (inverse ratio)	0·035(0·005)	0·10(0·031)†

Values are mean(s.e.m.). *$P < 0{\cdot}01$, †$P < 0{\cdot}05$ *versus* group 1 (Wilcoxon rank sum test)

Conclusion: These findings implicate Fas/FasL-induced apoptosis in pouchitis and introduce caspase inhibition as a novel therapeutic paradigm in this condition.

Molecular detection of lymph node metastases in patients with colorectal cancer

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Background: The widespread use of reverse transcriptase–polymerase chain reaction (RT-PCR)-based assays targeting tissue-specific markers does not identify the presence of cancer cells conclusively. This study aimed to correlate known tissue-specific markers with a tumour-specific alteration and improve current colorectal cancer (CRC) staging.

Methods: All primary tumours were screened for K-*ras* mutations using restriction endonuclease-mediated selective polymerase chain reaction (REMS-PCR). RNA was extracted from fresh lymph nodes harvested from patients undergoing colorectal resection for CRC or benign disease and subjected to quantitative RT-PCR (TaqMan) analysis. Three tissue-specific markers, carcinoembryonic antigen (CEA), cytokeratin 20 (CK20) and guanylyl cyclase C (GCC), were quantified. Lymph nodes obtained from patients with K-*ras*-positive tumours were screened using REMS-PCR.

Results: Seven of 23 primary tumours contained a K-*ras* mutation. GCC messenger RNA (mRNA) in histologically negative lymph nodes was associated with the detection of K-*ras* mutations, indicating the presence of genuine micrometastatic tumour cells. In these same lymph nodes, levels of CEA and CK20 mRNA were also illegitimately transcribed at high levels in 80 per cent of control lymph nodes. Conversely, only two of 101 control lymph nodes contained GCC mRNA.

Conclusion: In contrast to CEA and CK20, GCC mRNA in lymph nodes indicates the presence of genuine tumour cells, as confirmed by the finding of synchronous K-*ras* mutations. Quantitative detection of GCC mRNA may improve CRC staging, but the use of other tissue-specific markers needs caution. Certainly the presence of GCC mRNA potentially upstaged three of 19 N_0 tumours, although the biological significance of this finding needs to be validated.

Overexpression of thrombomodulin inhibits proliferation and growth of human pancreatic adenocarcinoma cells

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Background: Thrombomodulin is an endothelial cell surface glycoprotein which modulates the anticoagulant functions of thrombin. Loss of expression of thrombomodulin is associated with metastatic phenotype in cancers of the breast and oesophagus.

Methods: The human pancreatic cancer cell line MiaPaCa2 was transfected with the full-length thrombomodulin gene in sense orientation by means of the lipofectin transfection method. Surface thrombomodulin expression was measured by flow activated cell sorter analysis, and absolute cellular thrombomodulin content with a standard enzyme-linked immunosorbent assay. Cell proliferation was determined over 48 h by thymidine incorporation assay, and *in vivo* primary tumour growth by a standard immunodeficient mouse model after subcutaneous injection.

Results: Transfection with the thrombomodulin gene in sense orientation resulted in a 50-fold increase in total cellular thrombomodulin content. Wild-type MiaPaCa cells (empty vector transfected) demonstrated a threefold greater proliferation compared with thrombomodulin-transfected cell lines (5026 *versus* 1764 counts per million cells; $P = 0{\cdot}019$). Moreover, tumours derived from thrombomodulin-overexpressing cell lines grew more slowly in nude mice, with a mean of 180 days to first appearance of tumours and a further 88 days to subsequent killing of animals. Wild-type tumours reached these endpoints more rapidly, at 53 and 19 days ($P = 0{\cdot}01$).

Conclusion: These data indicate that thrombomodulin expression is associated with slower proliferation and growth of human pancreatic carcinoma cells and heightens interest in its role in tumour biology.

In vivo study of two new photosensitizers following interstitial photodynamic therapy of the liver

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Background: Photodynamic therapy (PDT) uses visible light and a tumour-localizing photosensitizer to destroy cancer tissue. Two new photosensitizers, temoporfin and a newer compound *meta*-hydroxyphenyl bacteriochlorin (mTHBC), were assessed *in vivo* to determine biological activity.

Methods: mTHBC was injected intravenously at doses of 0·15, 0·3, 0·6 and 1·2 mg kg^{-1} into two groups of two adult Large White pigs. Temoporfin was given at the dose of 0·15 mg kg^{-1}. Interstitial PDT of the liver was performed 24 h later. Six sites were irradiated at 740 or 652 nm at a light dose of 2–100 J cm^{-1} using a 2-cm cylindrical light diffuser at a power of 200 mW cm^{-1}. The treated areas were assessed 48 h after irradiation by macroscopic assessment.

Results: The volume of necrosis produced by mTHBC was 10·7 (95 per cent confidence interval (c.i.) 8·5–13·0) cm^3 with one interstitial application of light. This was significantly greater than the volume of necrosis of 1·8 (95 per cent c.i. 1·2–2·4) cm^3 achieved with temoporfin. The depth and volume of liver necrosis was dependent on both the mTHBC dose and the light dose employed. A strong positive correlation between the extent of necrosis and the log of the light dose was observed.

Conclusion: mTHBC is significantly more effective than temoporfin for interstitial PDT of the liver and represents the first demonstration of clinically useful volumes of liver necrosis produced by PDT applied using light from a single optical fibre.

Hepatic-mediated lung injury induced by pancreatitis is attenuated by Kupffer cell immunomodulation

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Background: Hepatic amplification of the inflammatory state in patients with acute pancreatitis has been implicated in the development of pulmonary injury. This study evaluated whether gadolinium chloride, an inhibitor of hepatic Kupffer cell activity, modulates the development of lung injury in patients with pancreatitis.

Methods: Pancreatitis was induced in 16 Sprague–Dawley rats by intraperitoneal injection of 20 per cent L-arginine (500 mg per 100 g body-weight), eight of which had also received 10 mg kg^{-1} gadolinium chloride 24 and 48 h before the induction of pancreatitis. Animals received normal saline (2 ml kg^{-1}) at 24 and 48 h. At 72 h, pancreas and lung pathology, pulmonary neutrophil infiltration (myeloperoxidase activity) and endothelial permeability (bronchoalveolar lavage and wet : dry weight ratios) were assessed. Values are given as mean(s.e.m.); the Mann–Whitney *U* test was employed for statistical analysis.

Results: Pulmonary neutrophil sequestration (2·0(0·1) activity units/g) and increased endothelial permeability (1694·3(460·5) &mgr;g/ml) were evident in the animals resuscitated with normal saline alone ($P < 0{\cdot}01$). However, both parameters were significantly reduced in the animals receiving gadolinium chloride ($P < 0{\cdot}04$). Lung injury score was also significantly diminished in the gadolinium chloride group (4·7(1·1) *versus* 1·8(0·9); $P = 0{\cdot}03$), whereas little difference was observed in the pancreatic injury score (5·3(1·3) *versus* 5·1(1·0)).

Conclusion: Pancreatitis-induced lung injury is mediated, at least in part, by hepatic Kupffer cells. Administration of gadolinium chloride attenuates the pulmonary insult, and this may be due to beneficial effects on Kupffer cell immunomodulation.

Patient education as part of a multifaceted strategy increases the detection of curable oesophagogastric cancer

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Background: Survival from oesophagogastric cancer is determined mainly by stage at diagnosis; most patients present with incurable disease. It was hypothesized that greater public awareness of potential cancer symptoms might improve early detection. A study was undertaken of the effect on stage distribution and resection rate of an intervention based on educational letters about cancer symptoms.

Methods: All patients aged over 40 years in 12 general practices (approximately 37 000 patients) were sent an annual letter for 3 years consecutively, asking them to report new symptoms of dyspepsia or dysphagia. General practitioners (GPs) were encouraged to refer these patients directly for gastroscopy. A control group (approximately 75 000 patients), matched for social class and age, received no education. Cancer incidence, stage and resectability were estimated from cancer registry and hospital records. Follow-up was continued for 6 years.

Results: Ninety-three cancers were detected in the study group, and 200 in the control group. Twenty-four (26 per cent) study and 30 (15 per cent) control patients had Union Internacional Contra la Cancrum (UICC) stage I–IIIA disease ($\chi^2 = 2\cdot77$, $P < 0\cdot1$).

Conclusion: Education of the public and involvement of the GP are associated with a 73 per cent increase in potentially curable cases of oesophagogastric cancer. This approach merits further large-scale study.

Cytokeratin 7 and 20 immunostaining in intestinal metaplasia of the distal oesophagus in patients with gastro-oesophageal reflux

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Background: Characteristic cytokeratin (CK) 7 and 20 immunostaining patterns differentiate intestinal metaplasia (IM) in Barrett's oesophagus from gastric IM; previous studies have shown 100 per cent concordance between patients with Barrett's oesophagus and those with the Barrett's CK7/20 pattern, and between patients with gastric IM and those with the gastric CK7/20 pattern. Gastro-oesophageal reflux (GOR) disease is associated with IM of Barrett's oesophagus, a premalignant condition, but less clearly with IM at the Z line in the absence of Barrett's oesophagus.

Methods: Fifty patients with 24-h pH studies included 34 with IM of the endoscopically normal Z line and 16 with IM in a short segment of Barrett's oesophagus (SSB): mean 1·5 cm (1 cm or more and 2 cm or less) columnar epithelium of the distal oesophagus with IM. Representative biopsies were avidin-biotin-peroxidase complex immunostained for CK7 (OV-TL 12/30, 1/1000; Dako, Ely, UK) and CK20 (Ks20.8 1/500; Dako, Ely, UK) following microwave antigen retrieval.

Results: Of 34 patients with an endoscopically normal Z line, ten of 14 had GOR disease and a Barrett's CK7/20 pattern, whereas only 11 of 20 without GOR disease had the Barrett's CK7/20 pattern. Of the 16 patients with SSB, nine of nine with GOR disease had a Barrett's CK7/20 pattern, and only three of seven without GOR disease had a Barrett's CK7/20 pattern ($P = 0\cdot035$, Fisher's exact test).

Conclusion: There is an association between GOR disease and Barrett's CK7/20 phenotype in both SSB and IM of the normal-appearing Z line. It remains to be seen whether follow-up screening is required in these groups.

Fasting gallbladder volume is increased after major non-gastrointestinal surgery

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Background: The formation of gallstones is increased after major surgery, including gastric and cardiac operations. Altered gallbladder motility may be a factor in allowing lithogenic bile to develop into a gallstone.

Methods: Patients having aortic ($n = 7$) and cardiac ($n = 13$) surgery had fasting gallbladder volume (a recognized indicator of gallbladder motility) measured before operation and after being established on a normal diet before discharge from hospital. Ultrasonography was used to make triplicate measures of gallbladder dimensions. The mean of each dimension was used to calculate gallbladder volume by the ellipsoid method. Local ethics committee approval of the study was obtained.

Results: Preoperative fasting gallbladder volumes were comparable in the two groups. Fasting gallbladder volume had more than doubled in the aortic group and tripled in the cardiac group.

	Aortic	Cardiac
Preop. volume (ml)	21·9 (15·2–43·6)	21·7 (6·3–50·2)
Diet commenced after operation (days)	4 (4–10)	2 (1–7)
Ultrasonography performed after operation (days)	8 (5–26)	5·8 (4–5)
Postop. volume (ml)	46·8 (32·0–103·3)*	70·0 (11·3–117·8)†

Values are median (range). *$P = 0\cdot007$, †$P = 0\cdot001$ *versus* preop. volume (Mann–Whitney U test)

Conclusion: Despite taking diet, fasting gallbladder volumes are increased in patients undergoing non-gastrointestinal surgery until at least the time of discharge from hospital. Altered gallbladder motility following operation may cause stasis, resulting in an increased incidence of gallstones in these patients.

Evidence of a role for leukotrienes in chronic pancreatitis in humans

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Background: Leukotrienes (LTs) are products of the lipoxygenase pathway and have a range of proinflammatory actions. To date they have been most studied in patients with chronic asthma. In addition their level is known to be raised in experimental acute pancreatitis and their antagonism has a beneficial effect.
Methods: LTE_4 was assayed in the urine of 20 patients with chronic pancreatitis (CP) and in 17 healthy controls. Enzyme immunoassay was employed, with correction for urinary creatinine. In addition, the DNA of 57 patients with CP and of 60 normal controls was analysed to assess any association with a known polymorphism in the promoter region of the LTC_4 synthase gene. Allelic frequencies were analysed with the test of proportions, and urinary LTE_4 levels with t, f and Mann–Whitney U tests as appropriate.
Results: Mean urinary LTE_4 concentration was significantly higher in patients with idiopathic CP compared with healthy controls ($P = 0{\cdot}04$). The 'C' allele of LTC_4 synthase was found in 46 per cent of chromosomes in patients with idiopathic CP, in 23 per cent of those with alcohol-induced CP and in 31 per cent of control chromosomes ($P = 0{\cdot}019$, idiopathic *versus* alcohol-induced CP; $P = 0{\cdot}066$, idiopathic *versus* control).
Conclusion: The LT pathway is activated in human CP, most prominently in patients with idiopathic disease. This group also has an increased frequency of the predicted high-production allele of LTC_4 synthase. These data suggest a role for the LT pathways in human CP and may warrant a trial of LT receptor antagonists (presently employed in patients with chronic asthma).

Ability of G17-DT to raise antibodies to G17 in patients with pancreatic carcinoma

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Background: Gastrin is thought to play a major role in the growth of pancreatic carcinoma. There is, therefore, a potential benefit from the administration of an antigastrin immunogen, gastrin-17-diptheria toxoid (G17-DT), to patients with carcinoma of the pancreas. Jaundice causes immune dysfunction that may affect the antibody response of patients with pancreatic carcinoma to G17-DT.
Methods: Three human pancreatic tumour cell lines, Pan 1, MiaPaCa2 and BxPC3, were characterized with respect to their expression of cholecystokinin B/gastrin receptors (CCKBR) and gastrin messenger RNA by real-time polymerase chain reaction analysis. G17-DT was administered to 26 patients with pancreatic carcinoma who were followed prospectively to assess G17 antibody production, side-effects and survival. These patients were both jaundiced and non-jaundiced. An immunoassay was performed to determine the ability of serum from G17-DT-immunized patients to inhibit iodinated gastrin from binding to CCKBRs on the rat pancreatic tumour cell line AR42J. Displacement was compared with that observed with rabbit antihuman G17 serum.
Results: Gastrin and CCKBR expression was confirmed in all three cell lines at gene level. G17-DT was well tolerated. Antibody production was not affected by a raised serum bilirubin level. The immunoassay confirmed that antibodies raised by these patients to G17 are as effective at displacing iodinated gastrin from CCKBRs as rabbit antihuman G17 serum.
Conclusion: This study demonstrates that G17-DT is effective at raising an antibody response to G17 in both jaundiced and non-jaundiced patients and may play a major role in the adjuvant treatment of gastrin-sensitive pancreatic carcinoma.

Interleukin 6 gene polymorphisms and the development of early organ dysfunction in patients with acute pancreatitis

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Background: Interleukin (IL) 6 is a pivotal proinflammatory cytokine with an established role in the development of organ dysfunction in patients with acute pancreatitis. The aim of the study was to determine the distribution of a G/C polymorphism at position − 174 of the IL-6 gene, to determine whether the G allele, which is associated with higher IL-6 production, is over-represented in patients who develop the severe form of the disease.
Methods: Patients with clinical and biochemical acute pancreatitis were included. The clinical course was charted prospectively by assigning multiple organ dysfunction syndrome scores on admission and for the first 7 days. DNA was extracted from peripheral leucocytes, polymerase chain reaction was performed, and alleles were resolved on a 3 per cent agarose gel.
Results: Sixty-three patients were included; 37 had no early organ dysfunction and 26 either presented with organ dysfunction or subsequently developed dysfunction within 7 days of hospital admission. No significant difference was seen in the distribution of the allele in the two groups ($P = 0{\cdot}207$, χ^2 test), and there was no difference in the frequency of the allele in patients with pancreatitis compared with controls.
Conclusion: The G/C polymorphism at position − 174 of the IL-6 gene is not associated with the development of early organ dysfunction in patients with acute pancreatitis.

Bacterial wall products enhance tumour cell proliferation and activate tumour cells directly

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Background: Bacterial translocation and bacterial wall products may enhance tumour growth following surgery for malignant disease. The direct effects of these products on tumour cells have not been investigated. The authors have shown previously that two ubiquitous bacterial wall products, endotoxin (lipopolysaccharide; LPS) and bacterial lipoprotein (BLP), enhance tumour cell proliferation, so they sought to determine the signal transduction pathways involved in this phenomenon.

Methods: The human colorectal adenocarcinoma cell line SW480 was incubated with culture medium, BLP (0·01–1 μg ml^{-1}), LPS (0·01–1 μg ml^{-1}) or LPS + BLP (0·01–1 + 0·01–1 μg ml^{-1}) for 24 h. Activation of nuclear factor (NF) κB was assessed by transfection of the luciferase reporter plasmid pNF-κB Luc Vector. The Renilla luciferase was used as an internal control. p38 kinase activity was assessed by Western immunoblotting. Proliferation was determined by bromodeoxyuridine assay.

Results:

	NF-κB lucerifase activity (RLU)
Culture medium	1·4(0·1)
BLP (1 μg ml^{-1})	2·0(0·1)*
LPS (1 μg ml^{-1})	2·7(0·1)*
BLP + LPS (1 μg ml^{-1})	2·5(0·1)*

Values are mean(s.e.m.). *$P < 0{\cdot}05$ *versus* culture medium (analysis of variance). RLU, relative light units

Tumour cell proliferation was increased after treatment with BLP, LPS and LPS + BLP. This correlated with an increase in NF-κB and p38 kinase activation.

Conclusion: Bacterial wall products enhance tumour proliferation; this may be through activation of p38 kinase and NF-κB. These findings endorse a role for the gut in the development of postoperative metastasis and may identify new therapeutic targets.

Pneumoperitoneum-induced tumour invasiveness is abolished by matrix metalloproteinase blockade

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Background: Matrix metalloproteinases (MMPs) are implicated in tumour metastasis. Exposure to the carbon dioxide pneumoperitoneum used in laparoscopic surgery can increase postoperative tumour growth. The effects of the pneumoperitoneum on MMP were examined, and correlated with tumour invasiveness.

Methods: Colonic (SW1222) and breast (MDA-MB231) adenocarcinoma cell lines were exposed to an *in vitro* pneumoperitoneum of carbon dioxide or helium at 3 mmHg or left in normal growth conditions (control). After 4 h exposure the ability of the cells to invade through 8·0-μm Transwell filters coated with Matrigel™ (Becton Dickinson, Franklin Lakes, NJ, USA) was analysed by colorimetric MTS assay. The effects of adding a known blocker of MMP, 1,10-phenanthroline (1,10-P), were also investigated.

Results:

	SW1222	MDA-MB231
CO_2	208(1·4)*	159(5·7)§
Helium	164(0·5)*	138(4·1)§
Control + 1,10-P	81(5·6)	98(0·4)
CO_2 + 1,10-P	92(5·5)†	100(3·7)†
Helium + 1,10-P	95(5·2)‡	103(4·1)‡

Values are mean invasion as a percentage of control. *$P < 0{\cdot}001$, §$P < 0{\cdot}05$ *versus* control; †$P < 0{\cdot}01$ *versus* carbon dioxide; ‡$P < 0{\cdot}01$ *versus* helium (Tukey–Kramer test)

Conclusion: Exposure of adenocarcinomas to either a carbon dioxide or helium pneumoperitoneum causes increased cell invasiveness, which is abolished by the presence of an inhibitor of MMPs. This suggests that MMPs have an important role in the metastatic potential of tumours exposed to an adverse operative environment.

Pathological response of breast cancers to primary docetaxel is predicted by human epidermal growth factor receptor 2 and oestrogen receptor status

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Background: Expression of the human epidermal growth factor receptor (Her) 2 has been shown to predict the susceptibility of breast cancer to doxorubicin and resistance to cyclophosphamide therapy. Docetaxel is increasingly being used to enhance response rates. This study correlated Her-2, oestrogen receptor (ER) and progesterone receptor (PR) expression with pathological response to primary docetaxel therapy.

Methods: Core biopsy specimens were taken from 35 patients before they received primary docetaxel. Tumours were typed and graded, and immunohistochemical examination for Her-2, ER and PR protein expression was performed. Operative specimens following completion of chemotherapy were assessed to determine pathological response.

Results: Univariate analysis revealed that ER negativity ($P = 0{\cdot}023$) and Her-2 positivity ($P = 0{\cdot}023$) distinguished patients with a complete pathological response. Multivariate analysis revealed that Her-2 positivity ($P = 0{\cdot}045$) and ER negativity ($P = 0{\cdot}01$) independently predicted which tumours would undergo a complete pathological response to docetaxel.

Conclusion: Breast cancers that express Her-2 oncoprotein and/or are ER negative can be identified as most likely to achieve a complete pathological response to primary docetaxel.

[^{18}F]fluorodeoxy-D-glucose positron emission tomography may predict the pathological response of breast cancer to primary chemotherapy

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Background: The aim of the study was to determine whether positron emission tomography using [^{18}F]fluorodeoxy-D-glucose (^{18}F-FDG-PET) can predict the pathological response of breast cancer to chemotherapy.
Methods: Patients with breast cancer destined to receive eight cycles of primary chemotherapy were enrolled into the study. PET imaging using 185 MBq ^{18}F-FDG was performed immediately before the first, second and fifth and after the last pulses of chemotherapy. Breast cancers were identified and ^{18}F-FDG uptake was calculated. Pathological response was determined by evaluation of the surgical resection specimens.
Results: To date, 50 patients have completed the study. Mean pretreatment ^{18}F-FDG uptake was not significantly different in responding and non-responding lesions ($P = 0.72$). Mean percentage change in ^{18}F-FDG uptake after the first pulse of chemotherapy was significantly greater in responding lesions ($P = 0.005$). There was no significant difference in ^{18}F-FDG uptake following the fourth or last cycles of chemotherapy in responding and non-responding lesions. Applying a 15 per cent change in ^{18}F-FDG uptake, PET following a single pulse of chemotherapy was able to predict pathological response with a sensitivity of 70 per cent and a specificity of 100 per cent.
Conclusion: ^{18}F-FDG-PET imaging of breast cancer following a single pulse of chemotherapy may be of value in the prediction of pathological treatment response.

Pretreatment predictors of survival in patients with locally advanced breast cancer treated with multimodality therapy

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Background: Multimodality therapy for locally advanced breast cancer has improved survival rates. However, many patients still have a poor prognosis. This study aimed to detect which patients were likely to have a poorer prognosis before commencing treatment. A range of factors related to the patient, the tumour, the acute-phase response and indices of immune function (natural cytotoxicity) were assessed.
Methods: Eighty patients with locally advanced breast cancer were treated with primary chemotherapy, surgery, radiotherapy and tamoxifen. They were followed for 5 years. The following factors were entered into a survival analysis: age, menopausal status, albumin level, C-reactive protein levels, CD56, natural killer cell activity, clinical tumour size and axillary node status.
Results: The 5-year survival rate was 72 per cent. Results of a multivariate (Cox proportional hazard) analysis of these factors revealed that reduced CD56 count ($P = 0.04$), increased clinical axillary nodal stage ($P = 0.04$) and a lower serum albumin level ($P = 0.002$) were independent predictors of patients with a poorer survival.
Conclusion: Pretreatment albumin levels, CD56 count and clinical axillary nodal assessment are independent predictors of survival in patients with breast cancer treated with multimodality therapy.

Objective measurement of breast cancer oestrogen receptor status through digital image analysis

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Background: A quantitative computer-assisted method of analysis of oestrogen receptor (ER) status in immunohistochemically stained sections in patients with primary breast cancer is described.
Methods: Paraffin-embedded sections from 40 patients with primary breast carcinoma were stained with anti-α-ER monoclonal antibody (1D5) using a standard immunohistochemical protocol. Images from ten high-powered fields were captured from each section using a digital camera mounted on a microscope at × 400 magnification and analysed with Adobe® Photoshop® image analysis software (Adobe Systems Incorporated, San Jose, CA, USA). A nuclear mask was obtained through the digital selection of nuclear area. Staining intensity in the nuclear mask was then analysed using red absorption characteristics. Digital three-layered analysis based on the technique used for obtaining histochemical scores (H score) was performed. Manual assessment of ER status was performed by counting the percentage of cells that are positive from 200 randomly sampled nuclei from ten high-powered fields. Correlation between the median optical density of the nuclear masks, the digital H scores and subjectively measured percentage positivity were expressed as Pearson correlation coefficients and confirmed by means of linear regression analysis.
Results: Of the 40 sections studied, seven were ER negative. The median percentage positivity in the remainder was 93 (range 17–100) per cent. Median digital H score was 175·6 (range 40–300). A close correlation was observed between median optical density of the nuclear mask and the H score for each section in both the red scale ($r = 0.89$, $P < 0.0001$) and the grey scale ($r = 0.82$, $P < 0.0001$). There was a significant correlation between percentage positivity and median H score

($r = 0.83$, $P < 0.0001$) and the median red scale of the nuclear masks ($r = 0.65$, $P < 0.0001$).

Conclusion: ER positivity can be assessed accurately by means of digital image analysis. This process offers objective data regarding the number of ERs within the nuclei, as well as the percentage of nuclei that express ERs.

Comparative genomic hybridization analysis of chromosomal alterations induced by the development of tamoxifen resistance

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Background: Tamoxifen resistance is a serious problem in the management of patients with breast cancer, and knowledge of the genetic pathways leading to tamoxifen resistance is important as it could allow the development of novel therapeutic strategies. This study aimed to determine the genetic changes between MCF-7, a tamoxifen-sensitive human breast cancer cell line, and its clone CL-9, which is resistant to tamoxifen, using comparative genomic hybridization (CGH).

Methods: DNA was extracted from MCF-7 and CL-9. The CGH assay was performed using: (1) MCF-7 DNA–normal placental DNA, (2) CL-9 DNA–normal placental DNA, and (3) MCF-7 DNA–CL-9 DNA. Images were captured with a charge coupled device camera and analysed by means of CGH analysis software. Metaphases were prepared from the cell lines and analysed by cytogenetics, and also by chromosomal painting for additional confirmation of amplifications and deletions.

Results: CGH analysis for the tamoxifen-sensitive and -resistant clone showed many areas of concordance, but important differences were seen in amplification of chromosomes 2, 3, 12 and 21, and deletion of chromosomes 6, 7q, 17p and 20. These findings were confirmed by cytogenetics and by use of whole chromosomal paints.

Conclusion: Transformation from a tamoxifen-sensitive to a resistant phenotype could be explained by changes at the molecular level. Definite alterations in the genetic profile were seen in the tamoxifen-resistant cell line involving regions harbouring potential genes (e.g. *p53*, *mdm-2*) that could be involved in the development of tamoxifen resistance.

Enhanced binding of tumour cells to mesothelium following exposure to pneumoperitoneum

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Background: Exposure to a carbon dioxide pneumoperitoneum in laparoscopic surgery can increase the occurrence of peritoneal metastases. For this to occur, cells must attach to the mesothelium. The effect of a carbon dioxide pneumoperitoneum on tumour cell–mesothelium interactions was analysed.

Methods: Primary cultures of human peritoneal mesothelial cells (HPMCs) were derived from omental samples. Monolayers of HPMC cells were exposed to either an *in vitro* carbon dioxide or a helium pneumoperitoneum for 4 h, or left under normal growth conditions (control). The ability of colonic (SW1222) adenocarcinoma to adhere to the monolayer was assessed. In parallel with these studies, alterations in mesothelial cell surface expression of $\alpha_v\beta_3$ and α_v integrin were analysed.

Results:

	Carbon dioxide	Helium
Adherence to mesothelium	141(10)*	136(8)*
Expression of $\alpha_v\beta_3$	200(20)*	198(16)*
Expression of α_v	122(7)*	111(2)*

Values are mean(s.e.m.) percentages of the control value. *$P < 0.05$ *versus* control (Tukey–Kramer test)

Conclusion: Exposure to either a carbon dioxide or helium pneumoperitoneum results in an increase in the ability of tumour cells to adhere to mesothelium. This indicates a mechanism whereby the operative environment influences tumour growth.

Soluble interleukin 6 receptor mediates colonic tumour cell adherence to vascular endothelium: a mechanism for metastatic initiation

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Background: Recent evidence suggests that endothelial adherence of tumour cells may be more important than transmigration in the formation of metastases. Soluble receptors of interleukin 6 (sIL-6Rs), shed by activated neutrophils following surgical injury, facilitate interleukin (IL) 6 adhesion-promoting effects on endothelial cells. This study examined the hypothesis that sIL-6Rs released by mediators of surgical stress increase tumour cell adherence to vascular endothelium.

Methods: Polymorphonuclear neutrophils (PMNs) were stimulated with lipopolysaccharide 100 ng ml^{-1} and C-reactive protein (CRP) 50 µg ml^{-1}. sIL-6R release was measured by enzyme-linked immunosorbent assay. Colonic tumour cells transfected with green fluorescent protein and endothelial cells were exposed to sIL-6Rs, and tumour cell adherence and transmigration were measured by fluorescence microscopy. Results are expressed as mean(s.e.m.) for five experiments; the Mann–Whitney *U* test was used for statistical analysis.

Results: Basal release of sIL-6Rs from PMNs was 44·7(8·2) pg ml^{-1} at 60 min. This was significantly increased by endotoxin and CRP (131·0(16·8) and 84·1(5·3) pg ml^{-1} respectively; both $P < 0{\cdot}05$). Endothelial and tumour cell exposure to sIL-6Rs increased tumour cell adherence by 71 per cent within 2 h ($P = 0{\cdot}04$) but did not significantly increase transmigration, even at 6 h.

Conclusion: These data identify sIL-6Rs as putative mediators in the genesis of early postoperative intravascular metastases.

Jugular venous neurone-specific enolase after carotid endarterectomy under local or general anaesthesia

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Background: Previous studies using near-infrared spectroscopy indicate that carotid endarterectomy (CEA) performed under local anaesthesia (LA) preserves cerebral cytochrome oxidase and autoregulation compared with surgery under general anaesthesia (GA). The hypothesis that LA offers a degree of protection against ischaemic injury was investigated by measuring ipsilateral jugular venous levels of neurone-specific enolase (NSE), a glycolytic enzyme released following cerebral injury, following CEA under both LA and GA.

Methods: Sixteen patients with symptomatic 70–99 per cent carotid stenoses were randomized (with ethics committee approval) to CEA with either LA ($n = 7$; mean stump pressure 48·5 (range 37–80) mmHg; zero of seven shunted) or GA ($n = 9$; mean stump pressure 49·1 mmHg; five of nine shunted). Jugular venous samples were assayed for NSE (immunoluminometric assay) before carotid clamping and at 5 min and 2, 4, 6, 8, 12 and 24 h after clamp release.

Results: There were no neurological complications. Mean (range) preclamp NSE levels were the same in both groups (LA 17·6 (15·2–20·7) µg l^{-1} *versus* GA 21·5 (11·3–26·2) µg l^{-1}; $P = 0{\cdot}44$). Peak levels occurred at 2 h (LA 24·8 (16·6–25·4) µg l^{-1} *versus* GA 48·2 (31·4–61·3) µg l^{-1}; $P = 0{\cdot}034$, analysis of variance), with a significant increase in patients having GA ($P = 0{\cdot}014$). NSE levels were higher in patients having GA at all time points up to 12 h, returning to baseline at 24 h.

Conclusion: This study suggests that CEA under LA is associated with reduced cerebral ischaemic injury compared with GA, and is consistent with niroscopic data indicating improved cerebral oxygenation in these patients. The case for a randomized trial of LA *versus* GA to assess differences in clinical outcome is therefore strengthened.

Association between intraplaque haemorrhage in the carotid atherosclerotic lesion, degree of internal carotid artery stenosis and timing of ischaemic neurological events

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Background: Expansion of a carotid atherosclerotic plaque as a result of intraplaque haemorrhage has been implicated in the development of ischaemic neurological events. The relationship between the amount of haemorrhage in the dominant atherosclerotic lesion, the degree of internal carotid artery (ICA) stenosis and the chronology of patients' symptoms was examined.

Methods: Consecutive patients undergoing carotid endarterectomy were included. The nature and timing of symptoms were recorded. Arch aortography was performed before operation. Carotid endarterectomy specimens were serially sectioned and examined histologically. The amount of intraplaque haemorrhage was measured by means of digital image analysis. Influence of timing of symptoms on the quantity of intraplaque haemorrhage was analysed by Kaplan–Meier analysis. Correlation between degree of ICA stenosis and amount of intraplaque haemorrhage was determined by regression analysis.

Results: Seventy-four patients (20 asymptomatic, 54 symptomatic) were included. Median latency of symptoms was 28 (range 1–600) days. Intraplaque haemorrhage was found in 54 (73 per cent) of 74 patients. Mean(s.e.m.) cumulative symptom-free survival before operation in patients with no intraplaque haemorrhage was 0·71(0·11), compared with 0·58(0·11) in those exhibiting haemorrhage in less than 50 per cent of plaque area and 0·2(0·07) in lesions involving more than 50 per cent ($P = 0{\cdot}002$). A close correlation was observed between the degree of ICA stenosis and the haemorrhagic content of the dominant atherosclerotic lesion ($r^2 = 0{\cdot}43$, $P < 0{\cdot}001$).

Conclusion: These results confirm the association between intraplaque haemorrhage and degree of ICA stenosis. They further demonstrate an association between the size of haemorrhage and the timing of neurological events, suggesting a causative role for intraplaque haemorrhage in the development of ischaemic neurological events.

Haemodilution effect of fluid management in abdominal aortic aneurysm surgery limits the effectiveness of acute normovolaemic haemodilution

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Background: Acute normovolaemic haemodilution (ANH) is said to conserve blood by reducing the net number of red blood cells (RBCs) lost with surgical bleeding. Infusion of large volumes of fluids required as standard anaesthetic management during abdominal aortic aneurysm (AAA) surgery contributes significantly to the intraoperative decrease in haemoglobin (Hb) concentration and may diminish the impact of ANH on red cell loss.

Methods: Patients undergoing elective AAA repair were randomized to undergo ANH or to act as controls. In patients having ANH a mean(s.e.m.) of 1020(70) ml of blood was withdrawn before incision and replaced with colloid. Other fluids were used as required. Hb concentration was determined in both groups before operation and before aortic clamping with blood loss of less than 100 ml.

Results:

	ANH ($n=15$)	Control ($n=17$)	P^*
Fluids at aortic clamping (ml)	3500	2000	< 0·001
Hb (g dl^{-1})			
Preop.	14·3	13·8	0·19
At aortic clamping	9·2†	11·0†	0·002

Values are median. *ANH *versus* control; †$P < 0·001$ *versus* preop. Hb (Mann–Whitney U test)

An estimated saving of only 50 ml or less of RBCs after 1000 ml blood loss can be achieved by using ANH in the above setting.

Conclusion: Large volumes of fluids used during AAA surgery reduce the loss of RBCs by the mechanism of hypervolaemic haemodilution, and the added benefit of ANH is limited by this effect.

Paracetamol absorption in the assessment of gastroduodenal function following aortic aneurysm repair

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Background: Early enteral feeding may reduce the incidence of multiple organ failure following repair of abdominal aortic aneurysm (AAA). The aim of this study was to determine, for the first time, whether paracetamol absorption can be used to assess return of gastroduodenal function, and so predict the timing of enteral feeding, in patients undergoing elective and emergency AAA repair.

Methods: Thirteen patients undergoing AAA repair (seven elective, six rupture) were given 1 g liquid paracetamol, via a nasogastric tube, 6, 18 and 32 h after operation. Plasma paracetamol levels were measured at 15, 30, 60 and 120 min afterwards. Absorption was determined by calculating the area under the curve (AUC-120).

Results: By 32 h, median (interquartile range) AUC-120 was three times greater in the elective group than in the rupture group (664 (462–754) *versus* 220 (213–274) mg l^{-1} min^{-1}), although the difference was not significant ($P = 0·2$, Mann–Whitney U test). Time to first successful enteral feeding was significantly shorter in the elective group (median 4 *versus* 9 days; $P < 0·01$, Mann–Whitney U test). There was a significant negative correlation between time to feeding and AUC-120 at 32 h ($r_s = -0·61$, $P = 0·026$).

Conclusion: Paracetamol absorption is a feasible means of assessing gastroduodenal function following AAA repair, and AUC-120 is closely related to the introduction of successful enteral feeding. Further studies, using the 32-h timepoint, to determine the relationship between paracetamol absorption, feeding and outcome are ongoing.

Lower limb revascularization improves calf muscle contractility

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Background: Physiological assessment of the severity of lower limb arterial occlusion by methods such as ankle : brachial pressure index (ABPI) or response to treadmill exercise, claudication distance (CD) and maximum walking distance (MWD) produces variable results which correlate poorly with function. Stimulated gastrocnemius muscle dynamometry (MD) eliminates cardiac, respiratory, locomotor and psychological variables.

Methods: Ten patients were studied 1 week before and 6 weeks after lower limb angioplasty to compare changes in ABPI, CD, MWD and MD. For MD, isometric gastrocnemius torque was measured during 5 min of stimulated contractions.

Results:

	Before angioplasty	After angioplasty	P
ABPI			
At rest	0·78(0·04)	1·02(0·06)	< 0·01
After exercise	0·57(0·06)	0·95(0·89)	< 0·01
CD (m)	55·3(12·6)	95·0(23·1)	0·14
MWD (m)	80·2(18·3)	119·3(24·7)	0·11
Final/initial torque (percentage increase)	23·5(7·4)	42·7(6·3)	< 0·05

Values are mean(s.e.m.)

Conclusion: Correction of lower limb arterial occlusion by angioplasty produces improvement in calf muscle function, which may be undetected by treadmill testing.

Are supervised exercise programmes clinically effective therapy for patients with intermittent claudication?

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Background: Supervised exercise programmes (SEPs) are recommended for claudication. This prospective observational study aimed to assess whether a SEP improves the quality of life (QoL) of claudicants.

Methods: Thirty-three claudicants (22 men and 11 women, median age 67 (range 49–77) years) attended a weekly SEP for 3 months. Patients were assessed before and at 1, 3, 6 and 12 months after starting the SEP with recording of: patient-reported maximum walking distance (PRWD); maximum treadmill walking distance (MTWD); ankle : brachial pressure index at rest (ABPI-R) and following treadmill testing (ABPI-PE). QoL was assessed using the Short Form 36 (SF-36) and EuroQol (EQ) instruments. SF-36 analyses eight individual QoL domains, while the EQ produces two QoL indices using time trade-off (TTO) data and a visual analogue scale (VAS).

Results:

	PRWD (m)	MTWD (m)	SF-36 pain	EQ VAS index
Before SEP	100	83	44	60
After SEP				
1 month	500*	108	61†	62
3 months	600*	208*	56†	70*
6 months	600*	208*	50	70*
12 months	600*	160†	50	65†

Values are median. *$P < 0.01$, †$P < 0.05$ *versus* before SEP (Wilcoxon matched pairs test)

No significant improvements in ABPI-R or ABPI-PE, in any of the other SF-36 QoL domains or in the EQ TTO index were found.

Conclusion: SEPs improve subjective and objective walking distances but result in only minor QoL benefits; furthermore, these benefits decline once the SEP is completed.

Scaling systems and disease severity in patients with the hand–arm vibration syndrome

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Background: There is an increasing requirement for accurate diagnosis and assessment of severity in patients with hand–arm vibration syndrome (HAVS). The aim of this study was to determine whether disease severity, as determined by the Stockholm Workshop Scale (SWS), is representative of underlying pathological processes as measured by objective methods.

Methods: Ninety-three patients (186 hands) with HAVS (91 men; median age 50 (range 28–74) years) underwent isotope limb blood flow (ILBF) measurements to determine hand perfusion, cold provocation thermography (CPT) to determine exaggerated vasoconstrictor response following exposure to cold, and two-point discrimination (TPD) aesthesiometry to determine sensorineural dysfunction. Results were compared with both normal values previously obtained within the department and with disease severity (SWS).

Results:

		SWS					
	Control	0	1	2	3	P†	P‡
ILBF hand (ml 100 ml^{-1} min^{-1})	36·36 (6·77)	25·25 (9·57)	23·21 (7·90)	23·30 (6·04)	23·81 (6·36)	< 0·001	0·8674
CPT fingertip (min)*	3·71 (1·64)	9·50 (1·27)	8·86 (1·95)	9·52 (1·30)	9·36 (1·56)	< 0·001	0·4994
TPD right hand (mm)	2·65 (0·80)	— —	3·74 (0·61)	5·42 (0·80)	5·00 (1·41)	< 0·001	0·0032

Values are mean(s.d.). *Time to return to rewarming temperature (min). †HAVS *versus* control; ‡objective tests *versus* SWS (one-way analysis of variance)

Conclusion: The SWS reflects sensorineural dysfunction but does not reflect the underlying vascular pathology. Objective investigations must be incorporated into disease classification scales to assess disease severity accurately.

Postural changes in tissue oxygenation in patients with venous ulcers

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Background: Tissue perfusion in venous ulceration has been studied previously in recumbent patients even though ulcers heal on elevation.

	Postural change in NIRS	
	Control (n = 11)	Ulcer (n = 20)
O_2Hb		
Dependent	+39(9)	+36(13)
Elevated	−26(9)	−23(8)
HHb		
Dependent	+45(7)	+52(10)
Elevated	−4(4)*	−36(9)*
HbD		
Dependent	−16(11)	−15(13)
Elevated	−20(7)*	+11(10)*
tHb		
Dependent	+76(7)	+95(88)
Elevated	−29(11)*	−60(16)*

Values are mean(s.e.m.). *$P < 0.05$

Methods: Twenty legs with chronic non-healing venous ulceration and 11 healthy control limbs were investigated with near-infrared spectroscopy (NIRS). Oxyhaemoglobin (O_2Hb), deoxyhaemoglobin (HHb), total haemoglobin (tHb) and oxygenation index (HbD) were measured for each 30 s during 3 min of elevation and 3 min of dependency.

Results: During elevation, the mean(s.e.m.) micromolar concentration of tHb and HHb fell by 60(15·5) and 36(9·2) μmol cm^{-3} respectively in ulcerated legs, compared with 29(11·6) and 3·9(3·9) μmol cm^{-3} in controls ($P < 0{\cdot}005$). HbD rose to + 11 in venous ulcers, compared with a fall of − 20 in controls ($P = 0{\cdot}021$). In dependency, HbD fell with greater significance in the ulcer group ($P < 0{\cdot}005$), indicating increased oxygen extraction.

Conclusion: In severe venous insufficiency, oxygen extraction increases during leg dependency, suggesting relative tissue ischaemia. This may be a cause of venous ulceration.

POSSUM and P-POSSUM in the comparative audit of patients undergoing carotid endarterectomy

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Background: The Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity (POSSUM) and the Portsmouth predictor equation for mortality (P-POSSUM) have been proposed as methods of risk adjustment to accommodate case-mix variation in vascular surgery. This study aimed to assess the predictive accuracy of POSSUM and P-POSSUM in the comparative audit of carotid endarterectomy (CEA).

Methods: Some 498 CEAs performed by four vascular surgeons from 1992 to 1999 in patients with a median age of 69 (range 38–86) years were analysed. Physiological and operative scores were calculated, with operative severity being graded as major plus. Individual predicted mortality was calculated using the POSSUM and P-POSSUM equations. Patients were then grouped according to predicted mortality. Linear and exponential analyses were applied to POSSUM and P-POSSUM predicted groups, and the ratio of observed : predicted deaths (O : P ratio) was calculated for each analysis.

Results: The overall observed 30-day mortality rate was 1·8 per cent (nine of 498 patients). Cause of death was stroke, myocardial infarction and heart failure in five, three and one patients respectively.

	POSSUM	P-POSSUM
Observed deaths at 30 days	9	9
Predicted deaths at 30 days	49	26
O : P ratio	0·18	0·35
P*	< 0·01	< 0·05

*χ^2 test

Conclusion: POSSUM and P-POSSUM cannot be employed usefully in the comparative audit of CEA because of gross overprediction of death. A model specific for CEA is needed to aid in the comparative audit.

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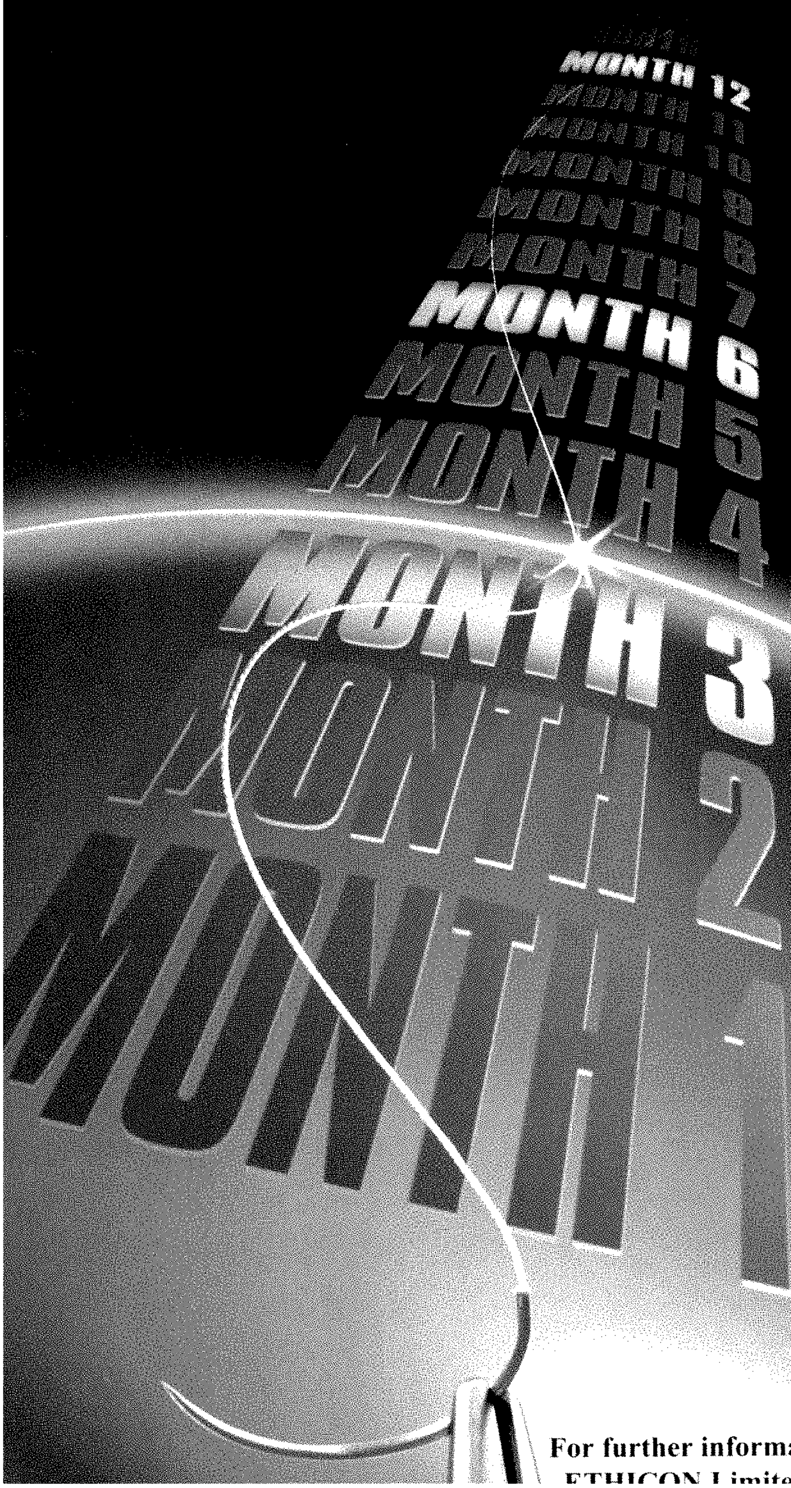

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The *BJS* ISSN 0007-1323

Published on behalf of the BJS Society. All queries regarding submitted papers not yet accepted for publication should be addressed to:
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Typeset and printed by Information Press Ltd, Oxford

*Periodicals postage is paid at Rahway, NJ and Additional Mailing offices. Postmaster: send address corrections to: *BJS*, c/o Mercury Airfreight International Ltd, 365 Blair Road, Avenel, NJ 07001, USA.

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Leading article

This is the first in a series of articles on ethics, professional governance and the law that BJS *will run through the remainder of 2001.*

Ethics in surgical practice

J. M. Little

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Surgical ethics may generally be considered as a special form of the ethics that applies to medicine in general. That is certainly the way in which McCullough *et al.* construe matters in their excellent book, *Surgical Ethics*[1]. They show how to apply principle-based ethics to surgical practice, and comment on special considerations surgeons may have to bring to bear on issues such as informed consent, confidentiality, emergencies, dying patients and personal biases against patients. Theirs is an immensely helpful and thoughtful book, which can be recommended to those seeking further enlightenment in this area.

Yet some surgeons have complained that, for all its excellence, there is something missing. I think that they are registering an absence of the voices and narratives of those who practise surgery and those who experience it. Surgeons and their patients are aware of the extraordinary nature of the surgical experience. Surgeons inflict a very particular kind of physical trauma in order to achieve something good. It is this trauma that distinguishes surgery from other medical endeavours. The procedural cardiologist and endoscopist, of course, may do traumatic things in order to achieve cure, diagnosis or palliation, but they proceed *per vias naturales*. The surgeon makes his or her way through the body's coverings on a scale unlike that of colleagues in other disciplines, such as interventional radiology. He or she relies on the wisdom of the body to heal wounds inside and outside more than colleagues in other specialties. To be on either end of this extraordinary transaction has some special characteristics. Ethics are about relationships and choices, and surgical relationships are defined by five characteristics that, while they may be present to some degree in other medical transactions, reach a special intensity in surgery[2,3]. Based on this centre's narrative research[4–7], one may call them: (1) rescue, (2) proximity, (3) ordeal, (4) aftermath and (5) presence. Rescue, proximity, ordeal and aftermath are *descriptive* of the experience of the surgical patient. Presence is something desired and desirable, and so is *normative*.

Rescue

Most people dread having operations. The physical assault, the breaching of the body's coverings, the pain, disability and risks are all things to be avoided if possible. Even minimal access surgery carries these connotations, miraculous though it seems to those who undergo it. If you seek surgery, therefore, you must perceive that you have or may develop something so threatening to your life, in its quantity or quality, as to justify the assault of surgery. You must, in short, seek a traumatic remedy in the face of a serious threat.

Proximity

By asking a surgeon's help, a patient enters a relationship of proximity like no other. By the end of the surgical encounter, the surgeon will know things about the patient's body that are hidden from the patient. He or she will have seen some way inside that body, and have observed its responses to injury and disease in ways that even the patient cannot share. The endoscopist, interventional cardiologist and radiologist have similar kinds of knowledge, but once again their approaches are less open, more 'natural'. This is not intimacy, which is mutual, but proximity, and it is an unbalanced and privileged relationship, which can be easily abused if it is not acknowledged.

Ordeal

The surgical encounter is an ordeal. It involves pain, anaesthesia, loss of autonomy, and constraints on space and time. It involves helplessness and dependence. It is something to be endured.

Aftermath

Surgical procedures leave scars, both on and in the body, and in the psyche. Bodily scars, stomas, stiffness, persistent discomfort and recurrent symptoms all serve as reminders of past or present illness, risk and threat. The survivors of serious illnesses such as cancer (in particular) carry psychosocial burdens from which they may never be free. The last skin clip or suture is not the end of the surgical story, nor does it end with discharge from hospital. The burdens of survivorship may be lifelong[4,7–9].

Presence

Not surprisingly, what patients want most from their surgeons is their presence. Given the ordeal they face, their need for rescue, the sense of proximity and privileged knowledge inherent in the surgical encounter, and the persistence of problems into the aftermath of surgery, people want their surgeon to demonstrate his or her commitment to a caring role by being there, aware of and responsive to the discomforts and fears attending illness and surgery. Surgery is so extraordinary as an act and a relationship that patients still expect something special from it. Anatole Broyard, dying from prostate cancer, tells what he wants of his doctor[10].

'I see no reason or need for my doctor to love me – nor would I expect him to suffer with me. I wouldn't demand a lot of my doctor's time. I just wish he would *brood* on my situation for perhaps five minutes, that he would give me his whole mind just once, be *bonded* with me for a brief space, survey my soul as well as my flesh, for each man is ill in his own way.'

Broyard points to the dimensions of presence for any doctor whose patient faces extreme experience. Much of surgery creates extreme experience, and the surgeon's presence – on rounds, visits, by telephone calls – is a reassurance and a support. Presence is both a virtue and a duty, and it can be taught. I question, as do Randall and Downie[11], whether one can teach communication skills, as if the performance of a protocol could stand in the place of personal insight and warmth. Even those who lack a degree of empathy, however, can be taught by precept and example that it is important to be present for surgical patients.

A surgical ethics

I suggest that an ethics of surgery can be constructed from an understanding of what goes on between those who experience surgery and those who practise it. Surgery creates extraordinary relationships between those who receive it and those who perform it. Understanding some of the peculiarities and intensities of that relationship helps us to get inside the vulnerabilities of our patients, and perhaps to understand something about our own vulnerabilities[7]. Even surgeons dread having surgery. Acknowledging the need – sometimes a desperate need – for rescue, the inevitability of the relationship of proximity, the nature of the ordeal of the surgical experience, the potential seriousness of the aftermath of surgery, and the patient's need for the surgeon's presence throughout the illness and beyond, will help us as surgeons to establish and maintain trust and a relationship of care with patients who are particularly vulnerable.

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Leading article

Resection margins in Crohn's disease

B. G. Wolff

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Soon after Crohn's disease was described in the early 1930s, surgeons began treating involved sections of bowel by resection and anastomosis. The point of reference at that time was bowel cancer, which also involved a focal segment of bowel and created enlarged lymph nodes in the mesentery. Of course this method of treating Crohn's disease by resection with 'curative' intent, similar to that for bowel malignancy, was based on an erroneous assumption. This stemmed from a lack of understanding that the disease is a process that can affect any part of the gastrointestinal tract; it is not merely a focal problem affecting only one section of bowel. This background explains the early importance of proximal and distal margins in surgery for Crohn's disease.

Time and surgical experience have shown that there is a high recurrence or relapse rate after resection for this condition. Some surgeons began to regard this relapse as almost inevitable, regardless of surgical technique. Others held that the problem was simply a result of inadequate clearance, and that a modification of surgical technique would lead to lower recurrence rates. Such a difference of opinion engendered the great debate on the importance of surgical margins in the 1980s. Krause *et al.*[1] in 1985 reported a long-term follow-up study of 186 patients divided retrospectively into two groups, one with a 'radical' resection of 10 cm or more of disease-free margins included in the resection specimen and the other with specimens with less than 10 cm of uninvolved bowel. Follow-up of more than 14 years showed that the group with the wider margins had a recurrence rate of 31 per cent and a better quality of life than the non-radical resection group which had a recurrence rate of 83 per cent. These dramatic results created much discussion and the study was criticized not only for being retrospective but also because the patient groups came from two different Swedish hospitals. Another retrospective study from Scandinavia provided a similar result in that patients with a margin of normal tissue of less than 4 cm (including those with histologically positive margins) had a recurrence rate that was ten times higher than that of a control group[2]. Nevertheless, a further retrospective study from the Uppsala region in Sweden, based on 353 patients undergoing a 'curative' resection from 1969 to 1986, suggested that the length of the disease-free resection margins did not influence recurrence rates in univariate or multivariate analysis[3].

The only prospective study examining this issue of length of uninvolved bowel was carried out by Fazio and colleagues at the Cleveland Clinic–Cleveland[4]. Patients undergoing ileocolic resection were assigned randomly to have a proximal margin of either 2 cm of grossly uninvolved bowel or 12 cm of uninvolved bowel. No *significant* difference in recurrence rate was found in the 56 patients undergoing extended resection in comparison to that of the 75 patients undergoing more limited resection, although the recurrence rate in the extended margin group was lower (18 *versus* 25 per cent). The question of statistical power in such a study is certainly an issue, but this is still the best information available at this time. The length of proximal margin was recorded in another prospective randomized study; patients with a length of 5 cm or more and less than 5 cm of uninvolved mucosa were compared, with no significant difference[5].

A separate issue is the margin that is histologically free of the mucosal changes of Crohn's disease or of non-specific inflammatory features. The above report by Fazio and colleagues[4] did not specifically address this question. For guidance one must look to retrospective studies but these have yielded disparate results. Several papers have suggested a benefit from a microscopically disease-free clearance at the margin for anastomosis while an equal number have shown no difference in terms of relapse rate. The controversial paper sparking this debate was published in 1980 by Pennington and colleagues[6]. A study from the Mayo Clinic showing different results was soon forthcoming[7] and a larger retrospective study from the Cleveland Clinic was published in 1991[8]. One interesting prospective randomized controlled trial by McLeod and colleagues[5] showed no difference between groups with and without marginal microscopic involvement. Importantly, this study may have made the issue of resection margins in Crohn's disease moot, in that prophylaxis after surgical resection has become accepted treatment by many gastroenterologists and surgeons, whether with mesalamine or immunosuppressive agents.

Is there anything in the realm of surgical technique that one can do to delay or prevent recurrence after resection of an isolated segment of bowel afflicted with Crohn's disease? Historically, the only factor of influence is that of proctocolectomy and Brooke ileostomy for Crohn's colitis. More recently, surgeons have retrospectively examined the technique of wide side-to-side stapled anastomosis for ileocolic disease *versus* the traditional end-to-end ileocolic anastomosis as a way of delaying the time interval to relapse (70–90 per cent of patients show endoscopic recurrence within 1 year[9]). Prospective randomized trials now under way in Europe and North America should provide an answer as to whether this manoeuvre has value.

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Review

Haemobilia

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Background: This review aims to establish whether increased use of invasive procedures and the trend toward conservative management of major trauma has resulted in an increased incidence of haemobilia.
Method: A Medline (http://igm.nlm.nih.gov/)-based search of the English language literature from January 1996 to December 1999 inclusive was performed using the keywords haemobilia, hemobilia, haematobilia and hematobilia. The presentation, aetiology, investigation, management and outcome of 222 cases were reviewed.
Results: Two-thirds of cases were iatrogenic while accidental trauma accounted for 5 per cent. Haemobilia may be major, constituting life-threatening haemorrhage, or minor; it may present many weeks after the initial injury. Diagnosis is most commonly confirmed by angiography. Management is aimed at stopping bleeding and relieving biliary obstruction; 43 per cent of cases were managed conservatively and 36 per cent were managed by transarterial embolization (TAE). Surgery was indicated when laparotomy was performed for other reasons and for failed TAE. The mortality rate was 5 per cent.
Conclusions: Although the incidence of iatrogenic haemobilia has risen considerably, the bleeding is often minor and can be managed conservatively. When more urgent intervention is required, TAE is usually the treatment of choice. There is no evidence that the conservative management of accidental liver trauma increases the risk of haemobilia.

Paper accepted 8 January 2001

British Journal of Surgery 2001, 88, 773–786

Introduction

The phenomenon of bleeding into the biliary tree, now known as haemobilia, was first recorded in 1654 by Francis Glisson, the Regius Professor of Physic in Cambridge from 1636 to 1637, in his treatize on the anatomy of the liver, *Anatomia Hepatis*[1,2]. He described a fatal case of haemobilia secondary to penetrating abdominal trauma sustained by a young man in a sword duel. The patient died 1 week following his injury. It was not until 1948 that Sandblom[2] first used the word haemobilia in his paper on haemorrhage into the biliary tree following trauma. Haemobilia is a rare condition that may be difficult to recognize but it is none the less important to include it in the differential diagnosis of gastrointestinal bleeding. Diagnosis is made easier when there is a history of liver trauma or instrumentation to direct attention to the biliary tree as a possible site of bleeding.

Haemobilia occurs when there is a fistula between a vessel of the splanchnic circulation and the intrahepatic or extrahepatic biliary system. The causes include iatrogenic and accidental trauma, gallstones, inflammation, vascular malformations and tumours. With the increasing use of percutaneous liver procedures there has been an increase in the incidence of iatrogenic haemobilia, such that this has become the most commonly reported cause. Furthermore, concern has been expressed that the trend toward conservative management of accidental liver trauma may result in an increase in the incidence of haemobilia from this cause[3].

Method

A Medline-based review of the English language literature waas carried out using the key words haemobilia, hemobilia, haematobilia and hematobilia. The publications between 1996 and 1999 revealed 222 reported cases of haemobilia[4–108], either as single case reports, small series usually following specific procedures, or within larger retrospective studies. Only a few cases were reported within the context of a prospective, randomized study[24,39], and only one of these studies investigated haemobilia as a discrete entity. The search was extended to include all previous reviews of haemobilia held on Medline, and specific publications between 1990 and 1995 that contribute additional information have been included. The reporting bias in a review of this nature will be considerable but, nevertheless, the authors believe that the results are an accurate representation of the current presentation, investigation and management of haemobilia.

Presentation

Quinke[109] described a triad of symptoms and signs with which haemobilia usually presents. These are upper abdominal pain, upper gastrointestinal haemorrhage and jaundice. All three may be present in up to 22 per cent of patients (*Fig. 1*). There are few causes of upper abdominal pain with gastrointestinal bleeding alone, and haemobilia must be considered in patients presenting with such a combination. There may also be cholangitis, with high fever and rigors. In major haemobilia the rate of bleeding is immediately life threatening. In minor haemobilia, although the blood loss is clinically significant, the patient is haemodynamically stable. If bleeding is brisk it may be confused with lower gastrointestinal haemorrhage[110]. Slow blood loss leading to chronic anaemia is an uncommon presentation, although it is of interest that faecal occult blood testing was once used as a diagnostic test in cases of biliary colic due to gallstones[111].

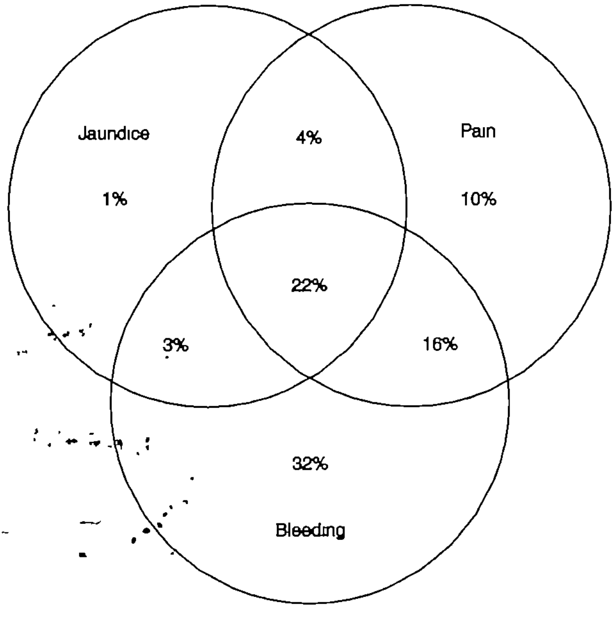

Fig. 1 Venn diagram of the presenting symptoms of 121 patients with haemobilia from a review of the literature from January 1996 to December 1999

The haemorrhage may be of rapid onset following liver trauma, or may be delayed by weeks. Occasionally it may be recurrent, with a prodrome of epigastric discomfort that is relieved at the onset of upper gastrointestinal haemorrhage. Previous reviews have found that 50 per cent of bleeding into the biliary tree is intrahepatic; the other 50 per cent is mostly from the extrahepatic bile ducts or gallbladder, and rarely the pancreas[112]. Risk factors for the delayed onset of haemobilia include bile stasis, hepatic necrosis and the formation of a slowly expanding pseudoaneurysm.

Blunt liver trauma is usually accidental, often due to road traffic accident. The shearing of arteries, veins and bile ducts without capsular rupture may result in an acute presentation of haemobilia. Associated parenchymal injury predisposes to bile stasis within a haematoma. Although the liver is well known for its powers of regeneration, contusions and lacerations in the presence of static bile do not heal. Bile has been shown to inhibit fibrin formation and granulation in liver wounds[113]. Healing may be further impaired by expanding pools of necrotic tissue within the liver parenchyma, which may eventually erode into hepatic blood vessels allowing fistula formation between them and the bile ducts, as seen in cases of blunt trauma. This results in delayed presentation of haemobilia.

Penetrating trauma, particularly following percutaneous instrumentation of the liver, is much less likely to cause cavitation but may still lacerate blood vessels and bile ducts, predisposing to immediate fistula formation and acute presentation of haemobilia. However, damage to a hepatic artery may result in a pseudoaneurysm which may expand until it erodes into the biliary tree, again resulting in a fistula. On the other hand, the damaged artery may form a true aneurysm and rupture much later. In the last two scenarios the presentation of haemobilia is delayed, sometimes by many months.

The fate of blood in the biliary tree depends on a variety of factors. Bleeding may be so rapid that the blood passes directly into the duodenum, appearing as haematemesis or melaena. When the haemorrhage occurs more slowly, blood and bile do not mix owing to their different specific gravities and surface tensions. The resultant clots obstruct the bile ducts[114]. A paradox exists that while bile is thrombolytic and may predispose to haemorrhage, the jaundice of haemobilia is due to bile duct obstruction by clot. The fate of these clots is variable. They may dissolve or be passed, or they may persist causing further bile stasis and exacerbating the situation. Further studies have shown that for bile enzymes to lyse fibrin there must be free flow of bile over the clots[115]. Decompression of the bile duct leads to both resolution of the jaundice and, in some cases, cessation of bleeding. Ultimately, clot may act as a nidus for the formation of pigment stones[26,44].

Haemobilia from a venous fistula is rare because of the high intraluminal pressure of an obstructed bile duct compared with the systemic venous pressure[48]. Patients with portal hypertension, however, are at risk, for example following placement of a transjugular intrahepatic portasystemic shunt[58,70]. Minor haemobilia seen in the tubing of percutaneous biliary drains may be venous in origin and should resolve when the drain is removed and the biliary pressure returns to normal. If bleeding is persistent the vessel may be tamponaded with a larger drain[116]. The process may be reversed with bile entering the blood stream directly through venous biliary fistulas and cases of bilhaemia have been reported, including fatal bile embolism following percutaneous biliary drainage[117].

Further complications of haemobilia are uncommon and include pancreatitis[9], cholecystitis[4] and cholangitis[118]. These are secondary to the haemobilia and must be differentiated from primary pancreatitis, haemorrhagic cholecystitis and cholangitis causing haemobilia. Pancreatitis secondary to haemobilia has a good prognosis once the haemorrhage has been controlled and it may be successfully managed conservatively[9,85,90]. Cholangitis following haemobilia may be severe and, although it is rarely reported, carries a high mortality rate even when treated aggressively with antibiotics and biliary drainage. Cholecystitis may occur early owing to the presence of haematoma in the gallbladder or later following on from the formation of pigment stones. In early cases immediate cholecystectomy is recommended, with T-tube drainage of the common bile duct to allow both biliary decompression and to wash out any remaining clots. Irrigation with saline may be considered.

Aetiology

The most commonly reported cause of haemobilia in the western world is now iatrogenic, mostly as a consequence of percutaneous liver procedures. The overall incidence of haemobilia is difficult to assess, as it is uncommon as a clinically significant entity. Careful investigation shows that it is often associated with gallstone disease; microscopic haemobilia occurs in up to one-third of such patients[114]. Sandblom[111] in 1972 reported 59 cases of haemobilia secondary to iatrogenic causes and 137 secondary to accidental trauma. The remaining cases were attributable to other causes. In 1981, Goodnight and Blaisdell[119] reported that trauma accounted for 50 per cent of all cases of haemobilia, with a ratio of iatrogenic to accidental trauma of 1 : 2. Since then there has been a shift in the pattern of aetiology (*Fig. 2*). Of the 222 cases in the present review 147 were iatrogenic in aetiology. Twelve followed non-iatrogenic trauma, most commonly road traffic accidents, and the remainder were from other causes (*Table 1*). Because of the inevitable reporting bias this is not an

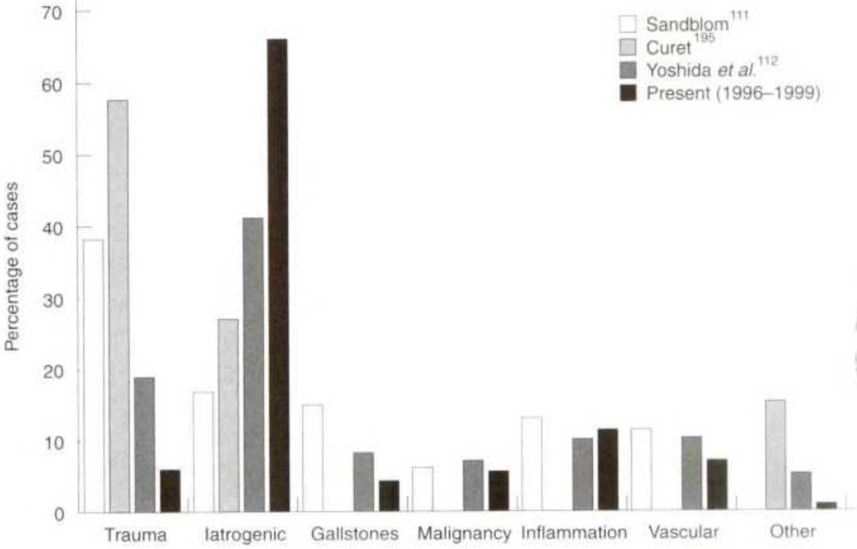

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Fig. 2 Aetiology of haemobilia from four reviews of the literature since 1972, showing an increase in iatrogenic causes, with a reduction in accidental trauma, as a percentage of the total

Table 1 Aetiology of 222 cases of haemobilia reported between January 1996 and December 1999

	No. of cases
Trauma	
Blunt	10 (5)
Penetrating	2 (1)
Iatrogenic	
Liver biopsy	30 (13)
Percutaneous transhepatic cholangiography	10 (4)
Percutaneous biliary drainage	43 (19)
Instrumentation	23 (10)
Cholecystectomy	29 (13)
Other surgery	4 (2)
Other procedures	9 (4)
Malignancy	
Cholangiocarcinoma	6 (3)
Hepatocellular carcinoma	6 (3)
Metastasis	2 (1)
Inflammation	
Gallstone disease	11 (5)
Acalculous cholecystitis	2 (1)
Ascariasis	1 (1)
Polyarteritis nodosa	2 (1)
Cholangitis	11 (5)
Vascular	
Coagulopathy	4 (2)
Vascular malformations	16 (7)
Other	
Pancreatic pseudocyst	1 (1)

Values in parentheses are percentages

accurate analysis of the distribution of causes of haemobilia, but it does reflect an increasing interest in this subject and an appreciation of the significance of the complications of percutaneous liver procedures. Previous reviews have put the proportion of iatrogenic haemobilia at 40–60 per cent, and from the present data the proportion of haemobilia caused by percutaneous procedures alone is 38 per cent.

In series examining percutaneous liver biopsy, the incidence of haemobilia following the procedure appears to lie between 0·06 and 1 per cent[112,120,121]. Within the context of such studies there are patients at greater risk, such as those with ascites (which prevents tamponade of the puncture site by the abdominal wall), coagulopathy (even when corrected for the procedure), cirrhosis (small livers allow other intra-abdominal structures to be hit) and liver transplant (the liver may be hypervascular and may lie in an abnormal position)[122]. Attempts have been made to reduce the incidence of complications by use of ultrasonographically guided biopsy[120], laparoscopic biopsy[123], transjugular biopsy[23] and biopsy with tract embolization[10]. Although the overall complication rate has been reduced by these techniques there is no reduction in the incidence of haemobilia. This is, perhaps, not surprising as haemobilia arises as a result of the accidental laceration of a hepatic artery, which is unlikely to be avoided by the above methods with the possible exception of tract embolization.

Simple logic suggests that the risk of causing significant damage to a blood vessel within the liver increases with the size of the needle; large needles are used for procedures such as percutaneous transhepatic biliary drainage (PTBD) and percutaneous transhepatic cholangiography (PTC). This is confirmed by the literature, with the greatest risk associated with PTBD in which case the problem is exacerbated by pre-existing bile stasis. The incidence of haemobilia following PTBD is between 2 and 10 per cent[21,24,124,125]. Techniques to avoid positioning the drain across major vessels may reduce this[14,40], for example avoiding insertion of the biliary drain into the biliary system close to the hilum of the liver where there is a high density of larger blood vessels in close proximity to large bile ducts[16]. In many cases minor haemobilia presents as blood in the drain tubing. This often stops when the drain is removed and no further investigation or treatment is required.

The incidence of haemobilia following PTC is up to 4 per cent[51], although this may be reduced with the use of fine-needle cholangiography[126]. The incidence of arterial injury on postprocedure angiography is much higher, 5 per cent following percutaneous liver biopsy and 4 per cent following PTC[127]. The incidence of arterial damage following PTBD is between 19 and 32 per cent[128,129]. Ultrasonographic guidance of PTBD may reduce the incidence of haemobilia[14]. Stenting of biliary strictures is associated with haemobilia in up to 10 per cent of procedures[22,130,131] and may be dramatic[132]. Lithotripsy, whether endoscopic or extracorporal, is associated with an incidence of haemobilia of up to 10 per cent[37,93,133,134]. Perhaps surprisingly, the reported incidence of haemobilia does not necessarily rise when lithotripsy is combined with stenting for hepatolithiasis[24,135].

Surgical exploration of the biliary tree for biliary stones may also cause haemorrhage as the intrahepatic ducts are in close proximity to the hepatic arteries[136]. Surgery of the hepatobiliary system may lead to haemobilia following injury to a hepatic artery by a suture needle, diathermy, clip or clamp. A pseudoaneurysm developing around the damaged vessel is the common lesion preceding the onset of haemobilia and the presentation may be delayed by many weeks. Concern has been expressed that laparoscopic cholecystectomy may have a higher risk of haemobilia than open cholecystectomy. Stewart *et al.*[137] reported five cases of haemobilia following laparoscopic cholecystectomy and four of these were as a result of traumatic aneurysm of the right hepatic artery. There have been 29 cases of haemobilia following cholecystectomy reported in the English language literature between January 1996 and

December 1999. Transarterial embolization (TAE) was successful in stopping bleeding in 23 cases but failed in three. Two patients died from uncontrollable haemobilia. Nicholson *et al.*[83] found nine cases following 1513 laparoscopic cholecystectomies. There is no evidence that there has been an increase in the incidence of haemobilia as this procedure has become more popular. Minor haemobilia following cholecystectomy may cause confusion on cholangiography, as clot in the common bile duct may be mistaken for residual stone. In 20 per cent of ducts explored for retained stone following cholecystectomy, clot rather than stone was found to be the cause of the filling defect seen on the operative cholangiogram[138].

Haemobilia following other operative procedures on the hepatic biliary system is rare, even following liver transplantation[139]. For liver transplant recipients the major risk factor for haemobilia is liver biopsy[122,140–143]. Should haemobilia occur, management decisions are more difficult as the transplanted liver is more reliant on the dual blood supply from the portal vein and hepatic arteries, and so less likely to tolerate anything other than superselective arterial occlusion (although the procedure may still be safely performed). Embolic occlusion of a major hepatic artery in a transplanted liver may result in hepatic necrosis, ischaemic cholangitis[44] or biliary stricture formation[144]. Haemobilia following hepaticojejunostomy[145], choledochoduodenostomy[146] and hepatic lobectomy[147] has been reported. Haemobilia caused by a T tube eroding into a hepatic artery has also been recorded, although it may be that the injury was sustained at the time the T tube was sited[136]. Iatrogenic clotting disorders following anticoagulation may also be associated with haemobilia[42,148].

Accidental damage resulting in haemobilia is usually secondary to blunt trauma and less often follows penetrating trauma, such as stab or gun shot injury (these injuries being less common). The incidence of haemobilia following major liver injury has been reported to be as high as 3 per cent in one series[3], but in other reports the overall incidence is 0·18 per cent or less[149,150]. Of 106 cases reviewed by Yoshida *et al.*[112] only one followed penetrating injury, but Croce *et al.*[151] reported that, of 482 patients with accidental liver injury, three cases of haemobilia followed blunt trauma and three followed penetrating trauma. Blunt trauma to the liver differs from penetrating injury in that a central rupture may leave a large cavity into which damaged bile ducts and blood vessels drain[152]. The resulting biloma or haematoma may continue to expand while liver healing is impaired. Necrosis of the cavity wall may cause erosion of adjacent structures. Risk factors for the development of haemobilia following trauma include the use of packs, formation of a central cavity and inadequate drainage[152,153]. If a hepatic laceration is explored, deep sutures should be used with care as these may cause further damage to bile ducts and blood vessels; superficial suturing of a deep laceration, on the other hand, may cause cavity formation[154].

The trend toward conservative management of liver injury might be expected to result in an increase in the incidence of haemobilia following accidental trauma[3], but recent reports show that this is not the case[150,155]. In three recent reviews of patients with severe liver trauma, 136 patients not requiring immediate life-saving surgery were managed conservatively without any haemobilia[156,157], and two of 135 patients with severe liver injuries developed haemobilia[107].

Extrahepatic causes of haemobilia following trauma must also be considered. The gallbladder is affected in up to 2 per cent of blunt abdominal traumas and haemobilia may follow such injury[158,159]. Gallstones are also associated with haemobilia, which may arise secondary to haemorrhagic cholecystitis or by a stone eroding into a blood vessel, usually the cystic artery[25,160]. Acalculous cholecystitis may also cause haemobilia[161–163].

Primary vascular anomalies may present with haemobilia, particularly hepatic artery aneurysm[8]. Angiodysplasia[164], arteriovenous malformation[88] and haemangioma are less common causes of significant haemobilia[165]. Patients with underlying coagulopathy are more susceptible although this may be treated by correction of the diathesis and adequate drainage[11,18,49,63]. Vasculitis has been reported to cause significant haemobilia, and may be associated with other connective tissue diseases[59].

Both primary and secondary[166–168] malignant tumours of the liver, bile ducts, gallbladder and pancreas occasionally present with haemobilia. This occurs when tumour invades the ductal system (which more often presents with obstructive jaundice). The rate of blood loss is rarely rapid, but it may cause anaemia. The presence of clots within the ducts can make cholangiograms difficult to interpret.

Parasitic infection by various organisms has been reported in association with haemobilia, including ascariasis[54] and hydatid[54], and should be considered in patients with a history of travel to endemic regions. Haemobilia may also complicate hepatic abscess and cholangitis[34].

Investigation

Investigation of a suspected case of haemobilia depends very much on the presentation and suspected aetiology. It must be remembered that haemobilia often presents days to months after an injury. For patients with upper gastrointestinal bleeding, oesophagogastroduodenoscopy (OGD) is the first investigation of choice. If blood or clot is seen at the papilla of Vater, haemobilia is likely to be the cause of the haemorrhage. However, as few as 12 per cent of these endoscopies may be diagnostic[112] and further investigation may be required.

The choice of subsequent investigation depends on the history and the level of suspicion. Goodnight and Blaisdell[119] in 1981 recommended OGD, computed tomography (CT) and then angiography for cases following trauma. Savastano *et al.*[169] investigated vascular parenchymal causes of upper gastrointestinal bleeding using OGD followed by CT then angiography, but all cases required angiography at some point. Angiography is now recognized as the definitive investigation, but many patients can be managed adequately on the basis of endoscopic and cholangiographic findings. Initial investigations may suggest haemobilia, which was confirmed by angiography in 59 per cent of cases. For those patients in whom endoscopy alone gives an adequate diagnosis and conservative management follows, further investigation is not normally performed. In the current series there were nine cases in which the haemobilia originated in the gallbladder and this was confirmed at laparotomy without further investigation. OGD was normal in 11 patients who were found to have haemobilia on further investigation. There were only two normal angiograms performed on patients subsequently found to have haemobilia, and this investigation, although not always necessary, is the gold standard for confirming the site and aetiology of haemobilia. Circumstantial evidence of haemobilia may be found using ultrasonography, CT and radioisotope studies.

Angiography was first used to demonstrate gastrointestinal bleeding in 1960[170] and can be expected to detect a vascular abnormality in over 90 per cent of cases of significant haemobilia[3]. As well as detecting active bleeding from an arteriobiliary fistula, an arterioportal fistula and false aneurysm may be seen. Technical difficulties may arise with anomalous origins of the hepatic artery or when there has been previous surgery and in some cases the angiogram may appear normal, particularly if the study is performed when there is no active bleeding[70]. The role of cholangioscopy in cases of haemobilia has not been clearly defined other than to investigate the aetiology[84]; it has been used in treatment[45,84].

Many patients presenting with haemobilia will have CT performed at some point, particularly those with blunt trauma to the abdomen, and active bleeding may be seen at the time of the investigation. Further evidence of active or recent bleeding into the biliary tree and gallbladder may be identified by pooling of contrast medium, intraluminal clots and biliary dilatation[13,161,171,172]. Although CT is not sensitive in detecting bleeding following liver injury, limiting its use as a first line of investigation for suspected haemobilia, it is specific and patients with CT evidence of arterial or venous injury require angiography[173]. Various risk factors for developing haemobilia can be identified including cavitating lesions, aneurysms and pseudoaneurysms. CT may be used subsequently to follow the progress of these lesions. 'Periportal tracking' is an area of low attenuation around segmental portal veins representing more subtle liver injury associated with an increased risk of developing haemobilia[174]. The CT grade of liver injury alone is not a good predictor of the development of subsequent haemobilia[157].

Ultrasonography of the liver for cases of suspected haemobilia is useful but may be misleading. One series included ten patients with haemobilia so investigated, of whom eight were reported as having normal bile ducts and the other two as having common bile duct cholelithiasis[175]. The reasons for these findings have been investigated[162,176,177]. Immediately following a bleed into the biliary tract there may be diffuse but high echogenicity similar to that of the liver itself, so that the bile ducts may not be seen at all. With the formation of clot from 24 to 48 h, a soft tissue mass may fill part of the duct with dilatation of the proximal duct. The clot then contracts, forming a tubular configuration conforming to the wall of the duct and the residual lumen may be mistaken for the true lumen. The evolution of diffuse hyper-reflectivity to less reflective masses strongly supports the diagnosis of haemobilia[178]. Aneurysm and pseudoaneurysm of the hepatic arteries may be noted as well circumscribed anechoic masses; although they are not necessarily pulsatile, Doppler ultrasonography may show flow within them, differentiating them from biloma or cyst[177]. Fresh blood clots within the gallbladder are highly echogenic. They appear as non-shadowing, non-mobile masses and changes of acute cholecystitis may be seen[162].

Cholangiography is useful if there is already percutaneous access or if endoscopic retrograde cholangiopancreatography (ERCP) is performed[28,175]. Blood may be seen refluxing down drainage catheters or at the papilla of Vater, and contrast studies may show filling defects in the biliary tree. The morphology of these defects is variable. String-like defects may occur if the clots have formed a cast of the biliary tree[28], or smaller spherical defects may be seen[118] (it is of particular importance to discriminate these from gallstones[89,138]). Aneurysm or pseudoaneurysm of the hepatic artery may cause indentation of the bile duct, and biloma may be noted[179]. Parasitic infection of the biliary tree may also be confirmed at ERCP[180].

The role of scintigraphic studies for the investigation of haemobilia is controversial. Although bleeding rates as low as 0·1 ml/h may be detected, the liver provides a large pool of radioisotope that obscures visualization of extravasation into the bile ducts. ^{99m}Tc-labelled sulphur colloid has a low background activity and is rapidly cleared by the reticuloendothelial system. However, this clearance results in high levels of isotope masking pathology in the bile ducts. ^{99m}Tc-labelled red blood cells (^{99m}Tc-RBCs) remain in the circulation for up to 48 h, making them useful for the investigation of intermittent bleeding. The higher background activity means that greater rates of bleeding are required if a bleeding point is to be demonstrated[170]. When used in the investigation of haemobilia, ^{99m}Tc-RBC scans can provide direct evidence of bleeding into the bile ducts[181–183] and indirect evidence by demonstrating localized 'hot spots' where isotope has been obstructed by clot in the intrahepatic bile ducts[184]. Haemorrhage into the gallbladder may also be seen[6,164]. If a cause for occult gastrointestinal bleeding is being sought, the liver should be included in the field to be studied. There is a role for scintigraphy in the investigation of suspected haemobilia if other investigations have proved normal.

Management

The management of haemobilia is directed at stopping bleeding and relieving biliary obstruction. Surgical intervention was first described in Kehr[185] in 1903, consisting of ligation of the right hepatic artery. In 1976 Walter *et al.*[186] reported the first successful TAE of a hepatic artery and, with recent improvements in selective catheters, this is now the first line of intervention to stop bleeding for most causes of haemobilia. Various approaches to biliary decompression have been described. The published evidence is in the most part anecdotal and descriptive. There are no randomized comparisons available but the cases series reviewed give a good guide to appropriate management (*Table 2*).

TAE involves the selective catheterization of a hepatic artery followed by embolic occlusion by autologous blood, balloon, microcoils, cyanoacrylate or Gelfoam (Pharmacia and Upjohn, North Peapack, New Jersey, USA). Previous reviews and retrospective series have shown the success rate of TAE to be 80–100 per cent[21,32,51,83,112,187]. The reported mortality and morbidity rates are lower than those after surgery[188]. A prospective study of TAE in 18 cases of haemobilia was undertaken by Horak *et al.*[32] using poly 2-hydroxyethyl methacrylate. Failure may be technical or due to the extensive collateral hepatic[143] and bile duct[101] blood vessels, and surgical facilities must be available[189]. The portal vein should be patent if arterial embolization is to be attempted[190] and hepatic sepsis is a relative contraindication for TAE[187]. Antibiotic prophylaxis is recommended if hepatic haematoma is present. Liver function is not usually compromised and liver enzyme blood levels return to normal after 6 weeks following a transient rise[191]. Death secondary to hepatic ischaemia following TAE has been reported[192], but the method has been used successfully even in some liver transplant patients in whom the portal flow has proved adequate. However, TAE must be recognized as a high-risk procedure in such patients[16]. Transcatheter arterial angiography with a view to proceeding to TAE is indicated for those cases of major haemobilia requiring blood transfusion, if bleeding is prolonged or recurs despite correction of coagulopathy, and in cases of minor haemobilia causing anaemia. It is also indicated if CT or ultrasonography indicates vascular injury. Because of the likelihood of rupture of aneurysms and pseudoaneurysms, their elective embolization is advised.

Table 2 Management of 171 cases of haemobilia reported between January 1996 and December 1999

Management	No. of cases
Conservative*	73 (43)
Embolization (including TAE)	61 (36)
Cholecystectomy	20 (12)
Other surgery	13 (8)
Expectant	2 (1)
Sclerotherapy/vasoconstrictors	2 (1)
Catheter compression (after PTBD)	1 (1)
Unsuccessful TAE requiring hepatic artery ligation	3 (2)

Values in parentheses are percentages. *Including correcting coagulopathy and adequate drainage.TAE, transarterial embolization; PTBD, percutaneous transhepatic biliary drainage

Surgery is indicated when TAE has failed, for cholecystitis, when there is hepatic sepsis and for failure to drain the biliary tree. Even if laparotomy is required for other pathology, TAE must still be considered as a first line of treatment for haemobilia. Ultimately the cause of bleeding and biliary obstruction may be dealt with at the same procedure[51,119]. Surgery for bleeding involves ligation of the bleeding vessel or excision of the aneurysm. When this cannot be identified, non-selective ligation of the right or left hepatic artery may be performed. If there is concern that the blood supply to the liver will be compromised, arterial reconstruction is indicated, bypassing the affected section of blood vessel using venous autograft or splenohepatic anastomosis[66]. If haemorrhage from collateral vessels continues even after ligation of the common hepatic artery[193], resection of the affected liver segment may be necessary. Further surgical options are dependent on whether the site of bleeding is intrahepatic or extrahepatic. If intrahepatic, such as following severe trauma or for tumour, partial hepatectomy may be necessary. Haemorrhage from the gallbladder and haemorrhagic cholecystitis require urgent cholecystectomy[29,77,80], as does cholecystitis following haemobilia[51,87,98,161,171].

Pancreatectomy and Roux-en-Y formation for extrahepatic bleeding has also been reported[35].

Although there are case reports of endoscopic coagulation of bleeding points this has not become accepted management[119]. However, it may be useful in cases of tumour bleeding when it can be combined with effective biliary drainage. There also exist case reports of vasopressin administration as a pharmacological method of stopping haemorrhage[24,76], but with limited success as the hepatic vasculature is less responsive than the rest of the splanchnic blood supply[170]. Somatostatin alone has been used successfully in haemobilia secondary to pancreatitis[194]. If the rate of blood loss is not significant, there is no evidence of significant underlying pathology such as aneurysm, and there is no bile duct obstruction, expectant management is appropriate[39,112,119]. If there is evidence of obstruction, endoscopic decompression may be used with or without nasobiliary drainage or stenting of the bile duct[51,131]. Series reviewing the management of haemobilia following PTBD recommend removal of the drain or passing a larger catheter[116] and irrigation of the bile ducts alone[51,128], but if this is not successful TAE will also be required[21,39,43,51].

When Sandblom's review of haemobilia was published in 1972, the mortality rate was at least 25 per cent[111]. By 1987 the reported mortality rate was 12 per cent[112]. There were five reported deaths from haemobilia in the 4 years 1996–1999, with a further six deaths from other causes shortly after otherwise successful management of haemobilia. Of those deaths resulting from haemobilia, one followed cholecystectomy[108]. A second patient died despite cholecystectomy and TAE following rupture of a pseudoaneurysm caused by cholelithiasis[77]. One patient with gallbladder carcinoma died after laparotomy[50]. Two died following conservative management (pancreatic carcinoma[104], polyarteritis nodosa[73]). The chronological reduction in mortality rate is a reflection of two factors. First, the incidence of minor haemobilia, usually iatrogenic in aetiology, has increased. This is often easily diagnosed, for example by the presence of blood in biliary drains, and it is these cases that explain the high proportion of resolution with conservative therapy. Second, improvements in the management of more significant haemobilia, particularly TAE, have resulted in lower mortality and complication rates than those associated with open surgery.

Conclusion

The diagnosis of haemobilia depends on the level of clinical suspicion. If actively sought, it will be found in a significant proportion of patients following hepatic instrumentation. Fortunately it only causes complications in a small number of patients. Urgent investigation of patients who are suspected of having significant haemobilia, using endoscopy and angiography, will confirm the diagnosis. Circumstantial evidence of haemobilia may be found with CT and ultrasonography. Angiography should be undertaken with a view to TAE, which is the first choice of therapy with a high success rate. If other conditions require operation, surgery remains an alternative, but TAE must still be considered as a means of minimizing the extent of the surgery required. Biliary decompression and restoration of bile flow past clots may also be necessary and this may be all that is required in cases of minor haemobilia. With the change in aetiology and the advent of new diagnostic and therapeutic techniques the mortality rate associated with haemobilia is low.

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Systematic review of antiplatelet therapy for the prevention of myocardial infarction, stroke or vascular death in patients with peripheral vascular disease

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Background: Antiplatelet agents may prevent vascular events and death in patients with peripheral vascular disease (PVD).

Methods: A systematic review of 39 randomized controlled trials of antiplatelet therapy in patients with PVD was performed.

Results: For patients with PVD the number suffering a non-fatal myocardial infarction, non-fatal stroke or vascular death in the antiplatelet group was 6·5 per cent compared with 8·1 per cent in the placebo group (odds ratio 0·78 (95 per cent confidence interval (c.i.) 0·63–0·96); $P = 0{\cdot}02$), favouring antiplatelet treatment. For infrainguinal bypass surgery (ten trials) and balloon angioplasty (two) the differences were still in favour of antiplatelet therapy, but they did not reach statistical significance. In five trials of aspirin against another antiplatelet agent, 8·4 per cent in the aspirin group suffered a vascular event compared with 6·6 per cent in the second antiplatelet group (odds ratio 0·76 (95 per cent c.i. 0·64–0·91); $P < 0{\cdot}01$), favouring ticlopidine/clopidogrel/aspirin + dipyridamole against aspirin alone.

Conclusion: Antiplatelet therapy reduces serious vascular events and vascular death in patients with PVD. For infrainguinal arterial surgery or balloon angioplasty the benefit remains unproven, but the number of trials to date is small. There is also evidence to support the use of antiplatelet drugs other than aspirin for the prevention of vascular events in those with PVD.

Paper accepted 26 January 2001

British Journal of Surgery 2001, 88, 787–800

Introduction

Peripheral vascular disease (PVD) is often complicated by ischaemic episodes occurring not only in the peripheral circulation but also in the coronary and cerebral vessels[1–4]. Despite the relatively benign prognosis for the affected limb, the symptoms of intermittent claudication are an indicator of systemic atherosclerosis[5]. Compared with age-matched controls, patients with intermittent claudication have a threefold increase in cardiovascular mortality rate[2,4,6,7]. The majority of patients with intermittent claudication are treated conservatively; smoking must be stopped and regular exercise is encouraged[8–11]. Antiplatelet treatment is given to reduce the risk of cerebrovascular and coronary events. Patients undergoing vascular interventions (e.g. surgical bypass, endarterectomy or percutaneous transluminal angioplasty (PTA)) are usually kept on antiplatelet treatment for the same reason, as well as to maintain graft and peripheral vessel patency[12,13].

Antiplatelet therapy (aspirin 75–325 mg daily) is effective in long-term secondary prevention of vascular events in patients at high risk of vascular disease, including those who have had an ischaemic stroke or acute myocardial infarction[12,14]. The benefit of aspirin therapy for patients with raised vascular risk has already been described in a recent meta-analysis by the Antiplatelet Trialists' Collaborative group (APTC)[12]. The APTC presented a meta-analysis of properly randomized trials that compared prolonged antiplatelet therapy (at least 1 month) against controls to establish efficacy, and trials that compared different antiplatelet agents. The present study augments the analysis presented by the APTC where necessary. The authors have reviewed trials published after March 1990 (the cut-off date for the APTC meta-analysis) assessing the impact of antiplatelet therapy in patients with PVD.

Clinical studies have demonstrated increased platelet aggregation in those affected by PVD[15–17]. However, it is not clear what the balance of risk and benefit of antiplatelet therapy is when given to such patients. Such treatment might reduce vascular death by reducing the incidence of cerebral and coronary thrombosis. However, antiplatelet therapy could also increase the risk of blood dyscrasias (e.g. ticlopidine) and gastrointestinal haemorrhage (e.g. aspirin), thus offsetting any benefits. There are also newer classes of antiplatelet drugs that do not act on the cyclo-oxygenase pathway and these have now been evaluated in large clinical trials. These drugs (e.g. ticlopidine, clopidogrel and the glycoprotein (Gp) IIb–IIIa blockers) have yet to make a major impact in the treatment of PVD, although they have been used extensively in association with coronary angioplasty and stenting. To assess the efficacy and safety of antiplatelet therapy administered acutely to patients with PVD, a systematic review was undertaken of all randomized controlled trials in this field.

Objective

The aim of this review is to provide evidence-based recommendations on the use of antiplatelet treatment for the prevention of cardiovascular events and stroke in patients with PVD. The effect of antiplatelet agents in reducing vascular mortality rates and cardiovascular events (myocardial infarction and stroke) was assessed in patients with PVD (Fontaine stage II) and in patients undergoing vascular intervention (surgery or PTA). Only antiplatelet agents whose principal mode of action is through inhibition of platelet aggregation or adhesion, or both, were included (*Table 1*). Agents known to have major vasodilating actions such as serotonin receptor antagonists (ketanserin), prostanoids (iloprost, beraprost), pentoxyfylline and naftidrofuryl were excluded. These drugs do not have a direct antiplatelet effect. Trials involving anticoagulants were not included.

Selection criteria

Studies

All double-blind and randomized controlled trials of antiplatelet treatment (aspirin, dipyridamole, indobufen, sulphinpyrazone, picotamide, suloctidil, ticlopidine and clopidogrel) *versus* placebo, or *versus* other antiplatelet agents, in patients with stable intermittent claudication or critical ischaemia (Fontaine stages II–IV) or undergoing vascular surgical intervention (surgery or PTA) were included. A randomized controlled trial was defined as a trial in which the subjects were assigned prospectively to one of two (or more) treatment arms by random allocation or by some quasi random method of allocation[18].

Table 1 Antiplatelet agents included in the analysis: the principal mode of action is through inhibition of platelet aggregation or adhesion

Mode of action	Antiplatelet drugs
Cyclo-oxygenase inhibitors	Aspirin, ibuprofen, indobufen, sulphipyrazone, triflusal
Phophodiesterase inhibitors	Dipyridamole
Platelet calcium channel ion inhibitors	Suloctidil
Thromboxane synthase inhibitors	Picotamide
Thienopyridine derivatives	Ticlopidine, clopidogrel

Participants

All patients with stable PVD (Fontaine stage II) for more than 6 months or patients undergoing vascular surgical intervention (surgery or PTA) for PVD[19] were included in the analysis.

Intervention

Either antiplatelet treatment (aspirin, dipyridamole, indobufen, sulphinpyrazone, picotamide, suloctidil, ticlopidine and clopidogrel) *versus* placebo, or one antiplatelet drug (aspirin) *versus* another antiplatelet regimen, were included. The antiplatelet or placebo intervention must have been given for at least 4 weeks; the type of therapy, dosage, time of starting and duration of therapy was recorded. Comparisons with exercise, anticoagulants or surgery were not included.

Outcome measures

The following outcomes were assessed: non-fatal myocardial infarction, non-fatal stroke and vascular/unexplained death. Significant gastrointestinal haemorrhagic side-effects were also included.

Data collection

Identification of trials

All relevant randomized controlled trials of antiplatelet agents for PVD that were available for review by January

1999 were identified. Studies that involved patients undergoing vascular surgical intervention were also included. The search strategy attempted to locate systematic reviews, meta-analyses and randomized trials using a combination of medical subheadings and free text searches from the following sources:

1. The National Library of Medicine's Medline database from January 1966 to January 1999.
2. Embase from January 1980 to January 1999 using the same terms.
3. The register of trials held by the APTC[12].
4. Cochrane Controlled Trials Register in the Cochrane Library (including Medical Editors' Trial Amnesty Database)[11].
5. Proceedings from vascular surgical society meetings (Vascular Surgical Society of Great Britain and Ireland, European Vascular Surgical Society, North American Society of Vascular Surgery).
6. The following pharmaceutical companies that market antiplatelet agents (ticlopidine, clopidogrel) were contacted for details of any trials, particularly unpublished ones: Bristol Myers Squibb, Sanofi Winthrop.

Methodological quality

The methodological rigour and clinical significance of each trial was assessed independently by each reviewer using the criteria used by the Cochrane Collaboration, with emphasis on concealment of randomization[20,21]. Each reviewer gave the trial an allocation score of A (clearly concealed), B (unclear if concealed), C (not concealed) or D (not used). Any discrepancies between reviewers in the above scores were discussed and a consensus reached. Trials scoring A for concealment of randomization were included, C and D excluded, and B discussed in detail (*Table 2*).

Outcome measures and data extraction

Data from the trials were independently extracted by two assessors and analysed using Meta-View version 4.0.3 (Update Software, Oxford, UK). Information regarding trial design, patient characteristics, dosages and duration of treatment was collected for each study. The data collected on each trial included information on the participants (age and sex distribution, assessment of claudication such as treadmill testing, ankle : brachial pressure index (ABPI) and type of surgical procedure where relevant), interventions (type and dosage of antiplatelet treatment and duration) and outcomes. Data relating to haemorrhagic side-effects were also collected.

The main outcome measures were: non-fatal myocardial infarction, non-fatal stroke or vascular death. Data on time to vascular event were not extracted. Data synthesis comprised a comparison of group results. Individual patient data from different trials were not amalgamated.

Statistical analysis

Data analysis was performed on an intention-to-treat basis using the groups that subjects were randomized to. In order to determine the size of the effect of antiplatelet treatment, the Peto odds ratio, relative risk and 95 per cent confidence intervals (c.i.) were estimated for each trial. Heterogeneity between trials was tested for using χ^2 tests; $P < 0{\cdot}05$ indicated significance. As long as statistical heterogeneity did not exist, a fixed effects model was used to calculate summary Peto odds ratios, relative risks and 95 per cent c.i.[21]. Where heterogeneity was found, a random effects model was used.

Description of studies

Thirty-nine randomized controlled trials fulfilled the initial criteria for consideration in this review[22–64] (*Table 2*). There were 24 trials of antiplatelet treatment *versus* placebo in patients with intermittent claudication[22–26,30,31,34–37,40,44–49,51,57,58,60–64] and ten trials of antiplatelet treatment *versus* placebo in patients undergoing lower limb bypass surgery[27,29,33,38,39,41,42,50,53–56]. There were two trials of antiplatelet treatment against placebo in patients with PVD undergoing PTA[28,43]. There were five trials of one antiplatelet treatment (aspirin) *versus* a second antiplatelet treatment in patients with PVD[32,45,52,57–59]. Two trials were included in the comparison of antiplatelet treatment *versus* placebo as well as in the comparison of antiplatelet treatment (aspirin) *versus* a second antiplatelet treatment as both of these trials had three study arms involving two antiplatelet treatments and placebo[45,57]. The description of these studies is summarized in *Table 2*.

The 24 trials of antiplatelet treatment *versus* placebo in patients with intermittent claudication involved a total of 6036 patients[22–26,30,31,34–37,40,44–49,51,57,58,60–64]. Ten trials of antiplatelet treatment *versus* placebo in those undergoing lower limb bypass surgery[27,29,33,38,39,41,42,50,53–56] involved 1765 patients, and two trials of patients undergoing PTA[28,43] involved 422 patients. Five trials of one antiplatelet treatment (aspirin) against another antiplatelet regimen (aspirin

Table 2 Characteristics of included studies

Reference	Year	Methods	Participants	Interventions	Outomes	Quality
Adriaensen[22]	1976	RCT, DB	30 patients with IC. Excluded: rest pain, tissue loss, coronary disease, hypertension	Suloctidil 100 mg tid *vs.* dihydroergotoxine 1·5 mg tid *vs.* placebo for 2 months	Pain-free walking distance and time, plethysmography (calf blood flow)	A
Arcan *et al.*[23]	1988	RCT, SB, PC, MC(30)	169 patients, with stable IC for > 12 months by treadmill testing. Confirmed by angiography	Ticlopidine 250 mg bd *vs.* placebo for 6 months	Maximum and pain-free walking distance, MI, stroke, TIA or deteriorating PVD	A
Aukland *et al.*[24]	1982	RCT, PC	65 men, stable IC for > 1 year	Ticlopidine 250 mg bd *vs.* placebo for 12 months	Maximum walking distance, ABPI and calf blood flow	B
Balsano and Violi[25]	1993	RCT, DB, MC(120) stratified, PC	2304 patients with IC, ABPI < 0·85	Picotamide 300 mg tid *vs.* placebo for 18 months	Vascular and non-vascular death, non-fatal MI and stroke, amputation	A
Balsano *et al.*[26]	1989	RCT, DB, PC	151 patients with stable IC for > 6 months. Confirmed by treadmill testing and ABPI	Ticlopidine 250 mg bd *vs.* placebo for 21 months	Maximum and pain-free walking distance, ABPI	A
Becquemin[27]	1997	RCT, DB, PC, MC(25) not stratified	243 patients after femoropopliteal/ tibial bypass with vein	Ticlopidine 250 mg bd *vs.* placebo for 24 months	Graft patency: clinical, ABPI, duplex and angiography. Death and major ischaemic events	A
Bergqvist[28]	1994	RCT, DB, PC MC(12)	223 patients undergoing PTA for IC or critical limb ischaemia	ASA 50 mg + Dip 400 mg *vs.* placebo for 3 months	Restenosis, ABPI and vascular events	A
Blakely and Pogoriler[29]	1977	RCT, DB, PC	137 patients with femoropopliteal bypass, 27 aortoiliac bypass	Sulphinpyrazone 600 mg *vs.* placebo, 36-month follow-up	Claudication distance and vascular events	A
Blanchard *et al.*[30]	1994	RCT, DB, PC, MC(21) stratified to diabetics and non-diabetics	615 patients with IC for > 12 months verified by treadmill testing	Ticlopidine 250 mg bd *vs.* placebo for 6 months	Sudden death, fatal and non-fatal MI or stroke, cardiovascular intervention	A
Bourde *et al.*[31]	1981	RCT, DB, PC	26 patients with ischaemic ulcers	Ticlopidine 1000 mg *vs.* placebo for 1 month	Thermographic index of ulcers	B
CAPRIE[32]	1996	RCT, DB, AC, MC(384) stratified by centre and subgroups	3 subgroups: stroke, MI or PVD. 6452 patients with IC, ABPI < 0·85, IC with previous leg amputation, bypass or angioplasty	ASA 325 mg *vs.* clopidogrel 75 mg for 12 months	Non-fatal stroke, MI, intracranial haemorrhage, amputation. Vascular death (stroke, MI, haemorhage) and non-vascular death	A
Castelli *et al.*[33]	1986	RCT, DB	50 patients undergoing thromboendarterectomy for occlusive disease	Ticlopidine 500 mg *vs.* placebo for 6 months	Patency by angiography, Doppler ultrasonography	B
Cloarec *et al.*[34]	1986	RCT, DB, PC	132 patients with IC	Ticlopidine 250 mg bd *vs.* placebo for 6 months	Treadmill testing and ABPI at 2-month intervals for 1 year	A
Colwell *et al.*[35–37]	1986 1989	RCT, DB, PC, MC(11)	231 men with NIDDM and a recent amputation for gangrene or active gangrene	ASA 975 mg + Dip 225 mg *vs.* placebo for 48 months	Death from vascular disease plus amputation of the opposite extremity for gangrene	A
Comberg *et al.*[38]	1983	RC, DB, PC	63 patients with femoropopliteal bypass	Sulphinpyrazone 800 mg *vs.* placebo for 6 months	Graft patency	B
Donaldson *et al.*[39]	1985	RCT, DB, PC	65 patients with femoropopliteal Dacron grafts	ASA 990 mg + Dip 225 mg *vs.* placebo for 12 months. 5-year follow-up	Maximum walking distance, ABPI, graft patency. Platelet aggregation/adhesion	B
Ellis[40]	1986	RC, DB, PC	203 patients with stable IC	Ticlopidine 500 mg *vs.* placebo for 6 months	Vascular and non-vascular death, non-fatal MI, stroke, TIA, surgery for PVD	A
Goldman and McCollum[41]	1984	RCT, DB, PC	53 patients with femoropopliteal bypass using Dacron/PTFE	ASA 900 mg+ Dip 225 mg *vs.* placebo	Occlusion, cumulative patency at 1 year	B
Green *et al.*[42]	1982	RCT, DB, PC	49 patients with infrainguinal. PTFE bypass	ASA 975 mg *vs.* ASA 975 mg + Dip 225 mg *vs.* placebo for 12 months	1-year graft patency, 3-monthly ABPI, vascular death, MI and stroke	A

Table 2 (continued)

Reference	Year	Methods	Participants	Interventions	Outomes	Quality
Heiss *et al.*[43]	1990	RC, DB, PC, AC	199 patients with >50% stenosis of femoropopliteal artery	ASA 990 mg+ Dip 225 mg *vs.* ASA 300 mg+ Dip 225 mg *vs.* placebo for 6 months	Walking distance, ABPI, plethysmography, angiography	B
Hess and Keil-Kuri[44]	1975	RC, PC	82 patients with IC	ASA 1500 mg *vs.* placebo	Platelet aggregation, vascular events	B
Hess and Keil-Kuri[44]	1975	RC, PC	176 patients with IC	ASA 1500 mg *vs.* placebo	Platelet aggregation, vascular events	B
Hess *et al.*[45]	1985	RC, DB, PC, AC	240 patients with stable IC	ASA 330 mg *vs.* ASA 330 mg + Dip 75 mg *vs.* placebo tid for 2 years	Arteriographic measurements at the beginning of the study and at 2 years	B
Holm *et al.*[46]	1984	RC, DB, PC	40 patients with stable IC	Suloctidil 300 mg *vs.* placebo for 9 months	Walking distance, calf blood flow and ABPI	A
Janzon *et al.*[47]	1990	RC, DB, PC, MC(6) stratified	687 patients with IC, previous amputation or bypass surgery for PVD	Ticlopidine 250 mg bd *vs.* placebo. Median follow-up 66 months	Fatal and non-fatal MI or stroke, TIA	A
Jones *et al.*[48]	1982	RC, DB, PC	40 patients with IC for > 6 months	Suloctidil 300 mg vs. placebo for 6 months	Walking distance, ABPI and muscle blood flow	A
Katsumura *et al.*[49]	1982	RC, DB, PC	193 patients with ischaemic ulcers	Ticlopidine 500 mg *vs.* placebo for 1 month	Mean diameters of ulcers, pain, granulation	A
Kohler *et al.*[50]	1984	RC, DB, PC	100 patients with infrainguinal bypass	ASA 975 mg + Dip 225 mg *vs.* placebo for 24 months	Graft patency	A
Krause[51]	1983	RC, DB, PC	38 patients with IC	Ticlopidine 250 mg bd *vs.* placebo for 3 months	Vascular and non-vascular death, non-fatal MI, stroke	B
Libretti and Catalano[52]	1986	RC, DB, AC	54 patients with IC	ASA 600 mg *vs.* ASA 600 mg + Dip 225 mg for 6 months	Pain-free walking distance, ABPI, plethysmography	B
Loew *et al.*[53–55]	1976 1977	RC, DB, PC, MC(2)	428 patients with infrainguinal bypass	ASA 1500 mg *vs.* placebo for 12 months	Graft patency	B
McCollum *et al.*[56]	1991	RCT, DB, PC. MC(48)	549 patients with femoropopliteal vein bypass	ASA 600 mg + Dip 300 mg *vs.* placebo for 34 months	Graft patency and cardiovascular events (MI or stroke)	A
Schoop and Levy[57,58]	1983 1984	RC, DB, PC, AC	300 men with IC, unilateral femoral stenosis	ASA 990 mg *vs.* ASA 990 mg + Dip 225 mg *vs.* placebo, 60 months	Angiographic stenosis at 24 months and non-invasive testing for 5 years	B
Schoop[59]	1983	RC, AC	62 patients with IC	ASA 1500 mg *vs.* ticlopidine 500 mg	Angiographic stenosis at 24 months and non-invasive testing for 5 years	B
Shaw[60]	1983	RC, PC	35 diabetic patients with IC	Ticlopidine 250 mg bd *vs.* placebo for 6 months	Diabetic ulcers, vascular events	A
Signorini *et al.*[61]	1988	RC, DB, PC	52 patients with IC	Indobufen 200 mg *vs.* placebo for 6 months	Pain-free walking distance	A
Steigler *et al.*[62]	1984	RC, DB, PC	43 patients with IC	Ticlopidine 250 mg bd *vs.* placebo for 12 months	Arteriography at the beginning of the study and at 12 months	B
Stuart *et al.*[63]	1980	RC, DB, PC	40 men with stable IC	Ticlopidine 250 mg bd *vs.* placebo for 2 months	Maximum walking distance, ABPI and calf blood flow	B
Verhaeghe *et al.*[64]	1981	RC, DB, PC	45 patients with IC	Suloctidil 300 mg *vs.* placebo for 6 months	Maximum walking distance, ABPI and calf blood flow	B

Quality refers to concealment of randomization: A, clearly concealed; B, unclear if concealed. RCT, randomized controlled trial; DB, double blind; PC, placebo control; AC, active control; MC(*x*), multicentre, where *x* shows the number of centres; ASA, aspirin; Dip, dipyridamole; bd, twice daily; tid, three times daily; *vs.*, *versus*; ABPI, ankle : brachial pressure index; IC, intermittent claudication; MI, myocardial infarction; NIDDM, non-insulin-dependent diabetes mellitus; PTA, percutaneous transluminal angioplasty; PTFE, polytetrafluoroethylene; PVD, peripheral vascular disease; TIA, transient ischaemic attack and dipyridamole, ticlopidine or clopidogrel)[32,45,52,57–59] contained 6928 patients with PVD.

Mortality data were available either from the published study or through contact with the authors. In 12 studies there were no deaths in either the antiplatelet or placebo groups[23,31,33,34,46,48,51,53,60,61,63,64].

Methodological quality of included studies

All studies were randomized controlled trials. In 21 trials a method of concealment was used that would be expected to reduce foreknowledge of treatment allocation (computerized randomization, pharmacy-controlled randomization or serially numbered sealed envelopes)[22,23,25–30,32,34,35,40,42,46–49,56,60,61]. Trials with adequate concealment of randomization were given allocation scores of A. However, in 18 trials concealment of allocation was unclear[24,31,33,38,39,41,44,45,51–55,57–59,62–64]. These trials were given an allocation score of B. These trials were reported as randomized but with no details on the method of concealment. There were no significant differences between the study groups in these trials. After discussion between reviewers these studies were included in the main analysis.

There were either no or minimal losses to follow-up in most trials. However, in the atherosclerotic disease evolution by picotamide (ADEP) trial there were 114 patients lost to follow-up[23]. This represented 5 per cent of the ADEP patients but there was no difference in percentage of patients lost to follow-up in the antiplatelet or placebo groups. In eight studies[27,32,44,48,50,51,56,59] patients lost to follow-up accounted for 5 per cent or less of the respective study populations. In four trials[24,39,46,64] patients lost to follow-up accounted for more than 10 per cent of the respective study populations.

Results

Antiplatelet drugs compared with placebo in peripheral vascular disease (*Table 3*)

There were 24 trials of antiplatelet treatment in PVD that met the inclusion criteria[22–26,30,31,34–37,40,44–49,51,57,58,60–64]. There was no significant heterogeneity between the 24 trials (*P* = 0·88). The pooled Peto odds ratio using a fixed effects model for vascular events was 0·78 (*P* = 0·02) favouring antiplatelet treatment in patients with intermittent claudication. For the incidence of death from vascular or unknown causes in patients allocated antiplatelet therapy the odds ratio was 0·75 favouring antiplatelet treatment. For non-fatal myocardial infarction the odds ratio was 0·97 but was not statistically significant. For the incidence of non-fatal stroke the odds ratio was 0·68 favouring antiplatelet treatment but just failing to reach statistical significance.

Antiplatelet drugs compared with placebo in lower limb bypass surgery (*Table 3*)

There were ten trials of antiplatelet treatment in lower limb bypass surgery that met the inclusion criteria[27,29,33,38,39,41,42,50,53–56] with no significant heteroge-

Table 3 Summary of results of antiplatelet drugs compared with placebo in patients with peripheral vascular disease (PVD) and patients with PVD undergoing lower limb bypass surgery or balloon angioplasty

		Events (*n*/total)		Heterogeneity			Fixed effects model	
	No. of studies	Antiplatelet agent	Control	χ^2	d.f.	*P*	Peto OR	*P*
Peripheral vascular disease								
Vascular events	24	202/3100	238/2936	10·51	16	0·88	0·78 (0·63–0·96)	0·02
Vascular death/not known	24	88/3100	110/2936	9·79	13	0·78	0·75 (0·56–1·01)	0·06
Non-fatal MI	24	78/3100	77/2936	9·85	11	0·63	0·97 (0·70–1·36)	0·90
Non-fatal stroke	24	36/3100	51/2936	13·49	10	0·26	0·68 (0·44–1·04)	0·07
Lower limb bypass surgery								
Vascular events	10	78/893	92/872	10·37	7	0·12	0·76 (0·54–1·05)	0·10
Vascular death/not known	10	46/893	53/872	12·68	7	0·12	0·80 (0·53–1·21)	0·50
Non-fatal MI	10	14/893	18/872	3·31	2	0·35	0·71 (0·35–1·44)	0·30
Non-fatal stroke	10	18/893	21/872	0·07	1	0·96	0·95 (0·68–1·32)	0·70
PTA								
Vascular events	2	7/240	6/182	0·21	1	0·90	0·73 (0·23–2·31)	0·60
Vascular death/not known	2	3/240	3/182	0·20	1	0·91	0·83 (0·16–4·28)	0·80
Non-fatal MI	2	3/240	2/182	0·20	1	0·91	0·75 (0·11–4·88)	0·80
Non-fatal stroke	2	1/240	1/182	0·07	1	0·90	0·48 (0·03–9·07)	0·60

Values in parentheses are 95 per cent confidence intervals. MI, myocardial infarction; PTA, percutaneous transluminal angioplasty; OR, odds ratio neity between the ten trials ($P = 0{\cdot}12$). The pooled Peto odds ratio using a fixed effects model for vascular events was 0·76 in favour of antiplatelet treatment but it did not reach statistical significance. For the incidence of death from vascular or unknown causes the odds ratio was 0·80 favouring antiplatelet treatment in patients after lower limb bypass surgery, but this again did not reach statistical significance. For the incidence of non-fatal myocardial infarction the odds ratio was 0·71, again favouring antiplatelet treatment but not reaching statistical significance. For the incidence of non-fatal stroke the odds ratio was 0·95 in favour of antiplatelet treatment but again this was not statistically significant.

Antiplatelet drugs compared with placebo in balloon angioplasty (*Table 3*)

In two studies involving patients with PVD undergoing PTA, seven (2·9 per cent) of the 240 patients allocated to the antiplatelet group suffered a vascular event[28,43] compared with six (3·3 per cent) of the 182 patients allocated to placebo. The pooled Peto odds ratio using a fixed effects model for vascular events was 0·73 ($P = 0{\cdot}6$) showing no significant benefit for antiplatelet treatment in this patient group.

Comparisons between different antiplatelet regimens in peripheral vascular disease

In five trials comparing one antiplatelet regimen against aspirin in patients with PVD, 292 (8·4 per cent) of 3467 patients in the aspirin group suffered a vascular event[32,45,52,57–59]. In the second antiplatelet regimen group (ticlopidine, clopidogrel or dipyridamole/aspirin combination), 227 (6·6 per cent) of 3461 patients suffered a vascular event. There was no significant heterogeneity between the five trials ($\chi^2 = 3{\cdot}49$, 4 d.f., $P = 0{\cdot}63$). The pooled Peto odds ratio using a fixed effects model for vascular events was 0·76 (95 per cent c.i. 0·64–0·91) favouring the second antiplatelet regimen in patients with PVD ($P = 0{\cdot}003$). The biggest effect was noted in the clopidogrel *versus* aspirin in patients at risk of ischaemic events (CAPRIE) study in which 215 (6·7 per cent) of 3223 patients in the clopidogrel group suffered a vascular event compared with 277 (8·6 per cent) of 3229 patients in the aspirin group. In this CAPRIE subgroup the odds ratio for vascular events was 0·77 (95 per cent c.i. 0·64–0·92) favouring clopidogrel ($P = 0{\cdot}0028$).

The incidence of death from vascular or unknown causes in patients allocated to receive aspirin was 130 (3·7 per cent) of 3467 patients. The corresponding total in the second antiplatelet regimen group was 104 (3·0 per cent) of 3461 patients. The pooled Peto odds ratio using a fixed effects model was 0·80 (95 per cent c.i. 0·61–1·03) favouring the second antiplatelet regimen group ($P = 0{\cdot}10$); this was not statistically significant.

The incidence of non-fatal myocardial infarction in patients allocated aspirin was 87 (2·5 per cent) of 3467 patients. The corresponding total in the second antiplatelet group was 52 (1·5 per cent) of 3461 patients. The pooled Peto odds ratio using a fixed effects model was 0·60 (95 per cent c.i. 0·43–0·84) favouring the second antiplatelet regimen group ($P < 0{\cdot}01$).

The incidence of non-fatal stroke in patients allocated to receive aspirin was 75 (2·2 per cent) of 3467 patients. The corresponding total in the second antiplatelet regimen group was 71 (2·0 per cent) of 3461 patients. The pooled Peto odds ratio using a fixed effects model was 0·95 (95 per cent c.i. 0·68–1·31) indicating no statistically significant difference between the two groups.

Adverse events

Overall there was no significant difference in the incidence of major bleeds between the antiplatelet and the placebo group. In 36 trials involving patients with claudication undergoing surgery or PTA in which antiplatelet treatment was compared with placebo, 47 of 4349 patients in the antiplatelet group had a major bleed[22–31,33–51,53–57,60–64]. In the placebo group 33 of 4100 patients had a major bleed. There was no significant heterogeneity between the 36 trials ($\chi^2 = 9{\cdot}3$, 13 d.f., $P = 0{\cdot}81$). The pooled Peto odds ratio using a fixed effects model was 1·40 (95 per cent c.i. 0·90–2·20) ($P = 0{\cdot}13$) indicating no significant difference in major bleeding between the antiplatelet and placebo groups.

In five trials involving patients with PVD in which one antiplatelet regimen was compared against another, 68 (2·0 per cent) of 3467 patients in the aspirin group suffered a major bleed[32,45,52,57–59]. In the second antiplatelet regimen group (ticlopidine, clopidogrel or dipyridamole/aspirin combination), 50 (1·4 per cent) of 3561 patients suffered a major bleed. There was no significant heterogeneity between these five trials ($\chi^2 = 4{\cdot}13$, 1 d.f., $P = 0{\cdot}13$). The pooled Peto odds ratio using a fixed effects model for major bleeds was 0·73 (95 per cent c.i. 0·51–1·06) ($P = 0{\cdot}1$) indicating no statistically significant difference in terms of major bleeding between the two groups.

Discussion

There is evidence that antiplatelet therapy protects a wide range of high-risk patients against vascular death, myocardial infarction and stroke[12]. The APTC presented a meta-analysis of randomized trials until March 1990 that compared 'prolonged' antiplatelet therapy for at least 1 month with placebo to establish the efficacy in several high-risk groups[12]. Further to that work, this review has identified five large randomized controlled trials of antiplatelet treatment in PVD involving over 9000 patients in total[25,27,28,30,32]. The ADEP[25] study was mentioned in the discussion of the APTC; however, it did not contribute to the main analysis, as these results were available after the deadline for that overview. The EMATAP[30] and Becquemin[27] studies both looked at the effects of ticlopidine against placebo in PVD. The CAPRIE[32] study is the only published study to date providing data on clopidogrel in PVD.

Aspirin is administered to patients with PVD to prevent death and disability from stroke and myocardial infarction[65]. Intermittent claudication is associated with underlying disseminated atherosclerosis that carries a twofold to threefold increase in cardiovascular mortality rate in comparison to age-matched controls[4,6,7,66]. The original meta-analysis from the APTC[14] of 31 randomized trials involving more than 29 000 patients with vascular disease convincingly showed that long-term aspirin therapy significantly reduced the overall vascular mortality rate as well as the incidence of non-fatal stroke and myocardial infarction. An update of this meta-analysis reviewed 174 randomized trials of antiplatelet therapy involving more than 100 000 patients[12]. Among high-risk patients, aspirin therapy was protective, reducing non-fatal myocardial infarction by one-third, non-fatal stroke by about one-third, and death from all vascular causes by about one-sixth. Sex, advanced age, hypertension and diabetes had no effect on this benefit. For all conditions, aspirin 75–325 mg daily was at least as effective as any other regimen, including higher-dose aspirin therapy which is more likely to cause side-effects and gastrointestinal complications[12].

The 1994 APTC report demonstrated the effectiveness of antiplatelet treatment[12], especially in patients with acute or previous myocardial infarction, stroke or transient ischaemic attack. Another 20 000 high-risk patients, representing a mixed category at risk of occlusive vascular disease (including the PVD subgroup), were thought likely to have a protective effect from aspirin. This was based on an overall result as there was no significant heterogeneity between the subgroups studied. However, the analysis of trials involving patients with PVD and those undergoing infrainguinal bypass surgery did not show a marked benefit. This observation suggests that in PVD antiplatelet therapy is not as effective as it is in other vascular risk groups. In the present review of 24 randomized controlled trials involving antiplatelet therapy in 6036 stable claudicants, antiplatelet therapy produced a 22 per cent risk reduction in vascular events. This is similar to the APTC meta-analysis findings in the 'high-risk group' of patients with clinically evident occlusive vascular disease. The recent North of England evidence-based guideline on the use of aspirin as secondary prophylaxis for vascular disease in primary care states that aspirin given to patients with intermittent claudication seems to have a small and statistically uncertain effect on the risk of a vascular event[67]. Evidence was reviewed from 23 randomized trials with the conclusion that aspirin for intermittent claudication was unlikely to have a beneficial effect on the subsequent incidence of non-fatal myocardial infarction, non-fatal stroke and death from vascular causes. Overall, the risk difference in favour of treatment was 1·3 per cent (95 per cent c.i. 0·1–2·7 per cent), a difference of borderline significance. A further conclusion was that patients with intermittent claudication who have additional indications of raised vascular risk (acute myocardial infarction, previous myocardial infarction, stable and unstable angina, and previous stroke or transient ischaemic attack) should benefit from antiplatelet treatment as secondary prevention.

In the present review, data from 24 randomized controlled trials show that there is a modest benefit from antiplatelet therapy in patients with stable PVD. Although antiplatelet treatment given in practice is usually in the form of aspirin (75–325 mg), the majority of the trials of antiplatelet therapy in PVD involved other antiplatelet agents (*Table 4*). The largest study, ADEP, contained 2304 patients and involved the use of picotamide which is not a commonly used antiplatelet agent[25]. Ticlopidine was the antiplatelet agent studied in 15 trials and suloctidil was studied in four trials. Only six trials studied the use of aspirin in PVD and most involved high-dose aspirin (975–1500 mg)[37,44,45,58,59]. One might wonder if low-dose aspirin would be less effective than the newer antiplatelet agents in patients with stable PVD but who still have an increased risk of myocardial infarction or stroke[6]. The use of low-dose aspirin in PVD cannot be based on direct evidence, only on analogy with coronary and cerebral atherosclerosis, for which it has documented efficacy[12,67].

Table 4 Antiplatelet agents and number of studies involved

Antiplatelet drugs	No of studies
Aspirin (± dipyridamole)[28,32,35–37,39,41–45,50,52–59]	15
Ticlopidine[23,24,26,27,30,31,33,34,40,47,49,51,53,59,60,62,63]	15
Clopidogrel[32]	1
Suloctidil[22,46,48,64]	4
Indobufen[61]	1
Sulphinpyrazone[29,38]	2
Picotamide[25]	1

The most recent trials have compared newer forms of antiplatelet therapy (clopidogrel, ticlopidine and picotamide) with placebo or aspirin. There was a benefit in favour of a combination of antiplatelet therapy (aspirin and dipyridamole) or a thienopyridine (clopidogrel or ticlopidine) *versus* aspirin alone. The largest effect was seen in the CAPRIE trial which compared the effectiveness of aspirin with clopidogrel in 19 185 patients with a mean follow-up of 1·9 years[32]. The patients had one of three main diagnoses: a recent ischaemic stroke, recent myocardial infarction or symptomatic PVD. Overall, clopidogrel was significantly ($P = 0{\cdot}04$) more effective than aspirin with a relative risk reduction for vascular events of 8·7 (95 per cent c.i. 0·3–16·5) per cent in favour of clopidogrel. Although CAPRIE was powered for an overall statistical analysis, a subgroup evaluation was also carried out. The results of the PVD subgroup in CAPRIE have been included in this review. In the CAPRIE-PVD subgroup, clopidogrel significantly ($P = 0{\cdot}0028$) reduced by 23·8 (95 per cent c.i. 8·9–36·2) per cent the relative risk of vascular events compared with aspirin. The incidence of fatal and non-fatal myocardial infarction was reduced by 37 per cent ($P = 0{\cdot}003$). Although the statistical interpretation is limited because the CAPRIE trial was powered for overall difference and not designed for subgroup analysis, the test for heterogeneity was positive ($P = 0{\cdot}042$). This indicates that the benefit could indeed be different among the patient subgroups. The patients in the CAPRIE-PVD subgroup had marked atherosclerosis, evidenced by the fact that 63 per cent had had arterial intervention previously and a mean ABPI of 0·57. The large number of participants in the CAPRIE-PVD subgroup provides evidence for a currently available alternative to aspirin in terms of endpoint effectiveness and safety[32,68]. There was overlap between the three clinical subgroups in the CAPRIE trial. For example, 11 per cent of the CAPRIE-myocardial infarction subgroup and 16 per cent of the CAPRIE-stroke subgroup had intermittent claudication. These patients, numbering over 1700, deserve further analysis[68].

Similarly, in the Swedish Ticlopidine Multicentre Study (STMS)[47], involving 687 patients with intermittent claudication followed up for 5·6 years, ticlopidine reduced the mortality rate by 30 per cent ($P = 0{\cdot}015$) compared with placebo. In the Becquemin study[27], involving 243 patients undergoing femoropopliteal/tibial bypass, 66·4 per cent were alive with a patent graft in the ticlopidine group compared with 51·2 per cent in the placebo group (95 per cent c.i. 2·9–27·4 per cent; $P = 0{\cdot}002$). In the EMATAP study[30] of 615 patients with intermittent claudication there was a statistically significant reduction of vascular events in the ticlopidine group compared with placebo (relative risk 2·93 (95 per cent c.i. 0·96–8·99); $P = 0{\cdot}043$).

Ticlopidine, which has a similar mode of action to clopidogrel, has been shown to be effective when compared with placebo. This is based on several randomized studies[26,27,30,47,69,70]. The APTC meta-analysis suggests that there is no difference between various antiplatelet inhibitors in terms of efficacy. However, it is difficult to match variables such as patient numbers, dosages, severity of disease and duration of treatment. Therefore, it is relevant to consider the double-blind randomized 'head to head' comparison in the CAPRIE study, between clopidogrel and aspirin. These results would be consistent with those of studies involving ticlopidine. The evidence from the STMS[47], EMATAP[30], Arcan[23] and Becquemin[27] studies suggests that ticlopidine is effective in PVD, where the use of aspirin may have some limitations. This is supported by trials of coronary stenting in which a combination of ticlopidine and aspirin was shown to be more effective in preventing major complications than aspirin alone[71,72]. Recent work suggests that the effectiveness of aspirin depends on the 'inflammatory' status of patients[73]. In apparently healthy males participating in the Physicians Health Study followed up for 8 years who later developed myocardial infarction, the use of aspirin (325 mg on alternate days) was associated with a significant risk reduction (55·7 per cent; $P = 0{\cdot}02$) among those in the highest quartile of baseline C-reactive protein (CRP) level[73]. In contrast, there was a non-significant risk reduction (13·9 per cent; $P = 0{\cdot}77$) among those in the lower baseline CRP quartile. Since CRP levels are raised in patients with PVD[74], it is likely that aspirin may not be equally effective in patients with different severities of disease.

Platelet inhibition is not a uniform process. Only some aspects of platelet activity are inhibited by aspirin, which acts mainly on endoperoxide synthesis, reducing thromboxane A_2 (TXA_2) release from platelets[65]. In contrast, ticlopidine and clopidogrel inhibit adenosine 5′-diphosphate (ADP)-induced platelet aggregation, which is a relatively aspirin-resistant process[75]. Clopidogrel also inhibits platelet aggregation induced by thrombin, TXA_2 and collagen[75,76]. This multiplicity of actions reflects the central role of ADP, TxA_2 and collagen[75,76]. ADP in particular (released from activated platelets) is of importance in mediating and amplifying the aggregation induced by several agonists.

The platelet activators affected by clopidogrel are of pathological relevance. ADP is released from damaged cells (e.g. erythrocytes) and by activated platelets[77,78]. Thrombin is a product of the coagulation cascade, and inhibiting its action on platelets is important in the prevention of thrombotic events[79]. Thrombin-induced platelet aggregation is relatively aspirin resistant[80]. The eiconasoid TXA_2, released by aggregating platelets, is a vasoconstrictor and promotor of platelet aggregation[81]. Collagen is present in the subendothelial layer and may activate platelets in blood vessels damaged by atherosclerosis[82].

Platelet hyperactivity has been reported in association with many clinical settings, including unstable angina, acute myocardial infarction, stroke, transient ischaemic attack, diabetes mellitus, cigarette smoking and hyperlipoproteinaemia[83,84]. Platelet adhesion and reactivity are increased in PVD despite the use of aspirin[15,85,86]. Platelet aggregation in whole blood has been found to be greater in those with PVD than in healthy subjects, and aspirin added *in vitro* does not significantly affect aggregation in PVD[16,17]. These studies show that aspirin-resistant platelet aggregation occurs in association with PVD. There may, therefore, be a group of patients with significant platelet hyperactivation and aggregation before any intervention despite concurrent aspirin treatment.

The increased effectiveness of clopidogrel compared with aspirin in the CAPRIE study may be related to the former's inhibition of ADP-induced platelet aggregation[68]. This form of platelet activation may be important in PVD and may explain the observed aspirin resistance in these patients. Some studies have shown that ticlopidine also improves other prothrombotic risk factors (e.g. plasma fibrinogen and serotonin) that are not altered by aspirin[24,87]. Since TXA_2 and ADP contribute to thrombogenesis, simultaneous inhibition of both pathways with clopidogrel plus aspirin might add significantly to the proven benefit of aspirin alone. Indirect evidence for the efficacy of the combination of aspirin and ticlopidine can be found from trials of coronary stenting[71,72]. The side-effect profiles of aspirin and clopidogrel were comparable in the CAPRIE study[32]. In particular the reduced neutrophil count, which occurs in a small percentage of patients taking ticlopidine, was not evident in those taking clopidogrel. In daily doses of 75–150 mg aspirin is cheap, has few side-effects and is effective at preventing major vascular events in patients at high risk of occlusive vascular disease. Any effects on vascular events with the addition of other antiplatelet agents, such as clopidogrel, may be modest but potentially worthwhile[88,89]. However, the reliable detection of such differences in patients with PVD may require large scale randomized evidence.

Aggressive risk factor (i.e. hypertension, hyperlipidaemia and diabetes mellitus) management has resulted in a reduction of vascular events in patients with previous myocardial infarction[90–92]. The previous trials of antiplatelet therapy in PVD should be evaluated in the setting of current clinical practice of cardiovascular risk factor management. The results of the CAPRIE[32], 4S[91] and cholesterol and recurrent events[90] studies suggest that future trials should establish whether simultaneous intervention, with several drugs acting on different targets, will reduce the incidence of vascular events more effectively than monotherapy.

The new generation of antiplatelet therapies being evaluated in coronary stenting and acute coronary syndromes are the platelet Gp IIb–IIIa blockers[93]. For example, the monoclonal antibody, abciximab, is a licensed product that prevents platelet aggregation[94]. This monoclonal antibody is administered intravenously and binds to the activated platelet surface Gp IIb–IIIa receptor, thereby preventing irreversible binding with circulating fibrinogen and von Willebrand factor. The binding of fibrinogen is the final common step in platelet aggregation. The role of Gp IIb–IIIa receptor blockade in vascular disease has not been fully established, but four parenterally administered Gp IIb–IIIa blockers (abciximab, eptifibatide, tirofiban and lamifiban) have been shown to reduce progression of disease in unstable angina and following percutaneous coronary stenting[95–98]. Three-year follow-up of patients with unstable angina from the first abciximab trials shows an overall reduction in mortality rate[99]. Several large trials evaluating prolonged treatment with oral Gp IIb–IIIa blockers are in progress[93,100]. However, early results from one trial of an oral Gp IIb–IIIa blocker (sibrafiban) against aspirin did not shown the expected clinical benefit[101]. The clinical indications for oral Gp IIb–IIIa blockers have yet to be established[102]. The efficacy of intravenous Gp IIb–IIIa blockers in clinical trials, all of which have included aspirin in both the control and experimental arms, suggests that aspirin monotherapy for platelet inhibition has now been improved upon[93]. Oral Gp IIb–IIIa blockers may produce significant benefits when used in addition to aspirin in high-risk patients. Trials are ongoing of prolonged oral Gp IIb–IIIa blockers given concomitantly with aspirin in patients with acute coronary syndromes[103].

Conclusion

Implications for practice

This review adds to the evidence from the last APTC meta-analysis on antiplatelet treatment in PVD[12]. Data from 24 randomized controlled trials show that there is a modest benefit from antiplatelet therapy in patients with stable intermittent claudication. In patients undergoing infra-inguinal surgery or PTA the benefit of antiplatelet treatment in preventing vascular events is unproven but the number of patients studied was small. However, the APTC study has shown that antiplatelet treatment is of value in maintaining graft patency; there are other reviews that specifically address the benefit of antiplatelet treatment in maintaining graft patency following lower limb bypass surgery[13,104]. There is more evidence to support the use of newer antiplatelet drugs, such as ticlopidine and clopidogrel, in the prevention of vascular events in PVD. Clopidogrel in particular has been shown to have a comparable side-effect profile to aspirin[32].

Implications for research

Scientific and clinical evidence for the simultaneous inhibition of TXA_2- and ADP-induced aggregation by aspirin and ticlopidine exists in studies of coronary stenting. More randomized evidence is required to establish the efficacy of clopidogrel and aspirin in combination, as well as any potential interactions or haemorrhagic complications, in the management of patients with PVD. It is likely that in the future patients at higher risk of vascular events will receive a second antiplatelet agent (an ADP receptor antagonist, a Gp IIb–IIIa blocker, or a combination of the two). An era of enhanced antiplatelet protection is coming; the major obstacles are the need to complete more clinical trials and the financial burden brought by these potent new drugs.

Acknowledgements

Supported by a *BJS* Research Bursary (1997).

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Randomized clinical trial of the effect of open *versus* laparoscopically assisted colectomy on systemic immunity in patients with colorectal cancer

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Background: Laparoscopic surgery is believed to produce an attenuated metabolic stress response and to have a less dampening effect on the immune response than open surgery. To date, the effect has not been studied in a randomized clinical trial of colorectal cancer.

Methods: The study was a two-armed randomized prospective trial conducted in parallel with the UK Medical Research Council's Conventional *versus* Laparoscopic-Assisted Surgery in Colorectal Cancer (CLASICC) trial comparing laparoscopically assisted colorectal surgery for left-sided tumours with conventional open surgery. Systemic immunity was assessed by determining the T- and B-cell counts, the CD4 : CD8 ratio, the natural killer cell counts, the immunoglobulin (Ig) G, IgM and IgA levels, and C3 and C4 levels. The white cell phagocytic activity (nitroblue tetrazolium test) was studied before operation and on the third postoperative day.

Results: A total of 236 patients were randomized in the immune study between 11 March 1997 and 14 August 1999; 161 had complete preoperative and postoperative assays for the analysis of results. There was no difference in mean response between the two surgical groups for each of the immune parameters studied. The unadjusted difference for the primary endpoint, T-cell count, 3 days after operation was – 1·6 per cent (95 per cent confidence interval – 5·0 to 1·8 per cent).

Conclusion: There is no difference in the systemic immune response in patients having laparoscopically assisted colectomy compared with those undergoing conventional open surgery for colorectal cancer.

Paper accepted 5 February 2001

British Journal of Surgery 2001, 88, 801–807

Introduction

Reduced hospital stay, less wound pain, earlier resumption of diet and earlier return of bowel function are recognized benefits of laparoscopic colectomy[1]. The minimal access technique is believed to produce an attenuated metabolic stress response and has a less dampening effect on the immune response, as has been shown in human[2,3] and animal[4–6] studies. This reduction is purportedly related to the smaller surgical incision. Theoretically, in the long term, the better immune status in the early postoperative period may translate into longer survival for patients with cancer[7].

The effects of laparoscopic surgery on the immune system differ from study to study, and its impact in cancer surgery is not known. Indeed, no published randomized trial to date has reported on the differential immune response following laparoscopy compared with conventional open laparotomy for colorectal cancer. In two published non-randomized trials of laparoscopic colonic resections for benign disease *versus* conventional open surgery[8,9], both studies showed an increased stress response as measured by a raised plasma interleukin (IL) 6 level, whereas an increased level of C-reactive protein (CRP) was evident in only one of the studies. Other trials of open *versus* laparoscopic cholecystectomy have not consistently shown beneficial effects on the immune system and the stress response. A reduced immune and stress response was seen in some studies[10–13]; in others there was no effect[14–18], while one showed a heightened response[8]. This inconsistency has been attributed to some extent to the small size and non-randomized nature of the studies[19]. The impact of laparoscopic colectomy for colorectal cancer on the immune system has not been studied in any randomized clinical trial. The aim of this randomized study was to determine the impact of laparoscopically assisted colectomy for colorectal cancer on systemic immunity.

Patients and methods

Trial design

This was a two-armed randomized prospective trial conducted in the Department of Colorectal Surgery, Singapore General Hospital, in parallel with the UK Medical Research Council (MRC) Conventional *versus* Laparoscopic-Assisted Surgery in Colorectal Cancer (CLASICC) trial in patients with colorectal cancer[20,21]. The local component of this collaboration investigated the immune stress response following open and laparoscopic resection for cancer. Patients with the clinical diagnosis of colorectal cancer based on colonoscopy or barium enema following histological confirmation were recruited. They were at least 18 years old and suitable for elective surgical resection by left hemicolectomy, sigmoid colectomy, anterior resection or abdominoperineal resection. Exclusion criteria were adenocarcinoma of the transverse colon, any contraindication to pneumoperitoneum, acute intestinal obstruction, any malignancy within the previous 5 years, synchronous multiple adenocarcinomas and pregnancy.

Randomization

Randomization was conducted through the central randomization office of the National Medical Research Council, Clinical Trials and Epidemiology Research Unit, Singapore, by means of a telephone call. Patients were entered into the trial based on a 1 : 1 treatment allocation to laparoscopically assisted or conventional open surgery after eligibility had been confirmed and informed consent given. Alternated randomized blocks of six and four were used to ensure treatment balance between the two arms after each ten consecutive patients. The treatment allocation was generated with a computer program.

Treatment

All patients were given bowel preparation by means of 2 litres of polyethylene glycol 1 day before operation without previous dietary restrictions or the use of antibiotics. Subcutaneous low molecular weight heparin was given 12 h before operation and at induction, a dose of metronidazole (500 mg) with either cefuroxime 1·5 g or ceftriazone 1 g was administered.

In the laparoscopic group, carbon dioxide pneumoperitoneum was created by means of the open technique in the subumbilical region (the camera port) with an insufflation pressure not greater than 12 mmHg. A 12-mm port was placed at the right (working port) and left iliac fossa region. A 5-mm port was placed at the left lumbar region and, if required, an additional 5-mm port was inserted in the right hypochondrial region. The peritoneum and especially the liver surface were examined carefully for metastatic deposits. The origin of the inferior mesenteric artery was isolated and freed from the ureter before division with the endo-stapler. Inferior mesenteric vein was taken at the same or a higher level. Mobilization of the sigmoid and descending colon was completed, dividing the lateral attachments. Further laparoscopic mobilization of the splenic flexure was performed if required. A suprapubic incision approximately equivalent to the size of the tumour was made for completion of the resection, to create the anastomosis under direct vision with an endoluminal stapler and to deliver the specimen. Total mesorectal excision was carried out via the incision for ultra-low anterior and abdominoperineal resections. In the open group, a standard oncological resection including total mesorectal excision was carried out where appropriate.

Immune studies

Some 30 ml of venous blood was taken from all the patients either 1 day before or on the day of the scheduled operation into two plain vacutainers, two ethylenediamine tetra-acetic acid (EDTA) vacutainers and one lithium–heparin vacutainer. These samples were sent immediately for processing on the same day. A second sample was taken on the third postoperative day. Serum C3, C4, immunoglobulin (Ig) G, IgM and IgA were assayed using immunonephelometry. B- and T-cell lymphocytes were assayed with 5 ml of EDTA blood by fluorescent flow cytometry. Specific surface antigens for the CD4 and CD8 subgroups were identified. Natural killer cell subsets were assayed with anti-CD56. White cell phagocytic activity was assayed by measuring their mitochondrial dehydrogenase activity in reducing 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide with phorbol-12-myristate-13 acetate stimulation (nitroblue tetrazolium test).

Statistical analysis

It was planned that the Singapore centre would recruit at least 200 patients for the UK MRC CLASICC trial. The change in T-cell count was identified as a major endpoint of the immune study. It was anticipated that the T-cell number in patients having open surgery would be reduced to approximately 25 per cent of the baseline value. It was hoped that the laparoscopic approach would result in T-cell counts being maintained at baseline levels or, at most, being reduced by 10 per cent. The difference in percentage reduction of 15 per cent would have a 95 per cent confidence interval (c.i.) of approximately 5–25 per cent based on a trial size of 200 patients.

Trial data were collected on printed forms, and subsequently entered into the COMPACT package[22]. All analyses were performed according to intention to treat, and the results were generated with SAS® version 6·12 software[23]. As a result, the incision lengths for the laparoscopic approach, for example, were included under laparoscopy in *Table 1* even when patients were converted to an open procedure. Analysis of covariance (ANCOVA)[24] was used to compare the treatment groups with respect to the major endpoint of T-cell counts and other secondary endpoints of humoral-mediated immune response, complement factors and phagocytosis functions. In particular, the cell-mediated immune response of CD4 and CD8 was analysed in terms of the ratio of these factors. Differences in treatment responses for these parameters were examined after making allowances for the baseline measurements. Prognostic factors such as Dukes' classification, tumour size, operating time and incision length were also considered in the modelling process.

Results

A total of 250 patients was entered into the Singapore component of the CLASICC trial between 11 March 1997 and 14 August 1999 (*Fig. 1*). As funding for this study was obtained 2 months after commencement of the CLASICC trial, evaluation of immune responses was possible in 236 patients. Thirteen patients (6 per cent) did not meet the eligibility criteria for the trial (eight laparoscopic, five open). Ten were found to have benign pathology on histological examination after operation. Two patients had other primary cancers (ovarian and lung) and another had a second cancer in the kidney.

Patient characteristics

Table 1 shows that the patients in both treatment arms were comparable in terms of demographic and clinical characteristics. Their median age was 63 (range 31–89) years. Eighty-five per cent underwent anterior resection. Eighty-eight per cent had a curative resection, and resection was

Table 1 Demographic and clinical characteristics of patients by treatment

	Laparoscopic (*n* = 118)	Open (*n* = 118)	All patients (*n* = 236)
Age (years)*	64 (33–87)	62 (31–89)	63 (31–89)
Sex (per cent)			
M	61 (52)	70 (59)	131 (56)
F	57 (48)	48 (41)	105 (44)
Operative procedure†			
Left hemicolectomy	5 (4)	6 (5)	11 (5)
Sigmoid colectomy	0 (0)	2 (2)	2 (1)
Anterior resection	98 (85)	100 (85)	198 (85)
Abdominoperineal resection	7 (6)	6 (5)	13 (6)
Other colectomy	6 (5)	3 (3)	9 (4)
Type of resection†			
Curative	99 (85)	104 (90)	203 (88)
Palliative	16 (14)	10 (9)	26 (11)
Irresectable	1 (1)	2 (2)	3 (1)
Dukes' classification‡			
A	9 (8)	8 (7)	17 (8)
B	45 (41)	50 (45)	95 (43)
C	42 (38)	43 (38)	85 (38)
'D'	14 (13)	11 (10)	25 (11)
Tumour size (cm)*	5 (2–10)	5 (1–9)	5 (1–10)
Operating time (min)*	88 (15–220)	70 (20–195)	80 (15–220)
Incision length (cm)	9 (1–40)§	15 (6–40)	12 (1–40)

*Values are median (range); other values in parentheses are percentages. †One patient defaulted on surgery in the laparoscopic group, and the operation was cancelled for two others (one laparoscopic, one open); data for one patient in open group with benign disease not included. ‡Histopathological examination was not performed for 14 patients because of non-malignancy, resection not done or treatment default. §Details of 15 patients who were converted to open surgery, and of another on whom the open approach was peformed by error, are given in the Results

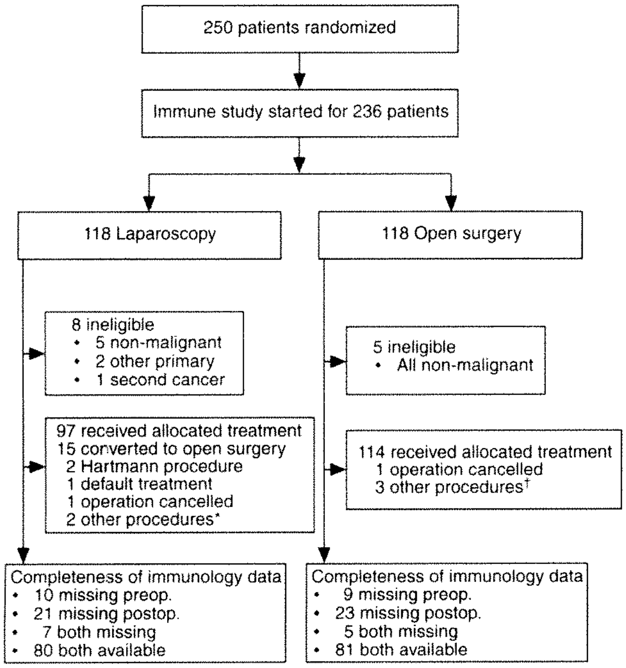

Fig. 1 Trial profile. *One procedure involved laparoscopic sigmoid colostomy, the other examination under anaesthesia and biopsy. †One local excision, one transverse sigmoid colon bypass, one loop colostomy

palliative for 11 per cent. The majority of tumours were Dukes' stage B (43 per cent) or C (38 per cent). No appreciable difference was observed between the tumour size of patients in the two treatment arms. The median surgical time for open operation was 18 min shorter than for the laparoscopic approach. The median incision length for patients in the open group was almost twice that for the laparoscopic procedure (15 *versus* 9 cm respectively).

Treatment compliance and complications

A total of 118 patients were randomized to laparoscopic surgery, and 15 had conversions to the open procedure (*Fig. 1*). The median operating time for these patients was 110 (range 50–220) min, compared with 85 (range 15–190) min for those who did not have conversion. Similarly, the median incision length for conversions to the open approach was 22 (range 9–40) cm, compared with a shorter length of 8 (range 1–24) cm for those who had no conversion. Two patients in the laparoscopic arm had a Hartmann procedure performed, one because of advanced cancer with perforation. In addition, two patients in laparoscopy group defaulted on treatment or had the operation cancelled, while two had other procedures involving laparoscopic sigmoid colostomy and examination under anaesthesia and biopsy. In the open group, the procedure was cancelled because of benign pathology in one patient. Other procedures, namely local excision of tumour, transverse sigmoid colon bypass and loop colostomy, were performed on three patients. Twenty-seven patients (16 laparoscopic, 11 open) experienced intraoperative complications and 13 (eight laparoscopic, five open) had postoperative complications (*Table 2*). The main intraoperative complication was significant haemorrhage requiring perioperative blood transfusion in 15 patients (6 per cent). Six postoperative wound infections were noted.

Table 2 Complications by treatment

	Laparoscopic	Open
Intraoperative		
Gross faecal contamination	1	3
Ureteric injury	1	1
Cardiac insufficiency	1	1
Surgical emphysema	1	0
Significant haemorrhage	7	8
Other	7	3
Postoperative		
Anastomotic leak	2	1
Wound infection	3	3
Intra-abdominal abscess	2	1
Pulmonary complications	0	2
Deep vein thrombosis	1	0
Urinary tract infection	0	1
Other	4	3

Immune stress response

Both the preoperative and postoperative immune response tests were omitted inadvertently in 12 patients. Nineteen patients had missing preoperative information, whereas a further 44 had missing postoperative immune response information. Thus analysis of the immune response included the remaining 161 patients with both preoperative and postoperative information available. The demographic and clinical profiles of patients with incomplete immune response information were similar between the two surgical arms (data not shown). Additionally, the mean measurements of each parameter for those with missing preoperative or postoperative information were no different from those with both measurements available. This occurred primarily for logistical reasons and thus has not caused any selection bias in the responses.

The initial measurements were identical between the treatment groups for all cellular and humoral mediated responses (*Table 3*). The T-cell response was the primary outcome of interest in the immune study. Statistical significance was not achieved for the unadjusted difference

Table 3 Comparison of mean immune response

	Normal range	Baseline*		Day 3*		Difference at day 3†
		Laparoscopic	Open	Laparoscopic	Open	
Cell-mediated response (%)						
T cell	51·3–71·1	63·5(12·2)	66·1(8·5)	63·8(10·5)	65·4(11·1)	– 1·6 (– 5·0 to 1·8)
B cell	11·3–29·3	14·2(7·2)	13·2(5·3)	15·3(6·6)	14·4(6·1)	1·0 (– 1·0 to 3·0)
CD4 : CD8 ratio	1·0–2·0	1·8(1·0)	1·8(1·1)	1·8(0·8)	1·9(1·2)	– 0·1 (– 0·4 to 0·2)
Humoral mediated response (g/l)						
IgG	7·3–15·4	12·0(2·8)	11·9(2·2)	10·1(2·8)	10·0(2·2)	0·1 (– 0·6 to 0·9)
IgM	0·3–1·5	0·9(0·4)	0·9(0·4)	0·8(0·4)	0·8(0·4)	0·01 (– 0·1 to 0·1)
IgA	0·7–3·8	3·0(1·3)	3·0(1·1)	2·7(1·2)	2·7(1·1)	– 0·01 (– 0·4 to 0·4)
Complement level (g/l)						
C3	0·5–1·3	1·1(0·2)	1·1(0·2)	0·8(0·2)	0·9(0·2)	– 0·08 (– 0·15 to – 0·01)
C4	0·2–0·7	0·3(0·1)	0·3(0·1)	0·2(0·1)	0·3(0·1)	– 0·03 (– 0·04 to – 0·01)
Phagocytosis function (%)						
Natural killer cell		10·2(8·0)	11·6(9·6)	11·3(7·1)	11·2(7·6)	0·1 (– 2·2 to 2·4)
NBT	63–90	92·1(13·8)	93·7(13·4)	89·9(16·3)	91·0(13·9)	– 1·2 (– 5·9 to 3·6)

*Values are mean(s.d.). †Unadjusted difference in mean values (laparoscopic – open); values are mean (95 per cent confidence interval). Ig, immunoglobulin; NBT, nitroblue tetrazolium test

in T-cell count 3 days after operation (95 per cent c.i. – 5·0 to 1·8 per cent; *P* = 0·35). The conclusion remained after taking into account baseline T-cell counts (*P* = 0·91). The adjusted mean T-cell response for patients randomized to receive laparoscopic surgery was a marginal 0·2 per cent higher than with the open approach (95 per cent c.i. – 2·5 to 2·9 per cent).

There was no difference in mean responses between the two groups. The only marginal differences were the C3 (unadjusted mean difference – 0·08 g/l (95 per cent c.i. – 0·15 to – 0·01 g/l); *P* = 0·03) and C4 (unadjusted mean difference – 0·03 g/l (95 per cent c.i. – 0·04 to – 0·01 g/l); *P* = 0·01) complement levels. Statistical significance was not achieved for these comparisons after adjustment for multiple testing using the Bonferroni correction[25]. Dukes' classification, tumour size, wound length and operating time had little influence on postoperative T-cell count and other immune parameters. The results were not affected after accounting for these possible prognostic factors and the respective baseline values.

Discussion

This trial has shown comparable complications between the two surgical groups (*Table 2*). Minimal access surgery is known to be associated with shortened hospital stay, reduction in postoperative pain and earlier resumption of normal function. This outcome has been hypothesized to be related to the lesser degree of tissue injury (i.e. incision length), surgical metabolic stress and immunosuppressive response with laparoscopic compared with open surgery[26]. While experiments in animal models have demonstrated a reduction in surgical metabolic stress and immunosuppressive response in laparoscopic surgery, parallel observations have not been consistently made in clinical trials. The results of this trial have shown that laparoscopic surgery has a comparable impact on the immune response to the conventional open procedure, with respect to the measured parameters. Marginal differences were seen in complement levels (C3 and C4), with the laparoscopic group evoking a lesser response than the open group. Previously published studies[8–14,16–18] with no more than 30 patients in each group were non-randomized, except for one hernioplasty trial[15] with 60 patients in each group.

The use of separate significance tests for each immune endpoint comparison increases the risk of a false-positive result. With ten comparisons between surgical arms, one significant difference might be expected even if the two procedures were identical. Thus, with the Bonferroni correction[25] applied by multiplying every *P* value by a factor of 10, the number of endpoints tested, statistical significance was not achieved for any of these comparisons.

Laparoscopically assisted colectomy generally differs from conventional surgical injury in the longer duration of anaesthesia, the need for a pneumoperitoneum, and the size of the abdominal skin incision. The median operating time for laparoscopic surgery was slightly longer: 88 min *versus* 70 min for the open procedure in the present trial. It is possible that the reduction in immunosuppression in the laparoscopic resections may be attenuated by the longer duration of anaesthesia with this approach. Such an observation has been reported in similar trials by Stage *et al.*[8] and Fukushima *et al.*[9], where laparoscopy took almost one and a half times longer than conventional open operation. Both these studies reported raised IL-6 levels and, in the latter study, an increased level of CRP. The median length of the abdominal wound incision for the laparoscopic operation was 9 (range 1–40) cm, compared with the larger median incision length of 15 (range 6–40) cm for the open approach. This difference in wound length did not have any effect on the systemic immune parameters measured in the study. In many ways, both surgical approaches have similar visceral dissection, mobilization and anastomosis. It may thus appear logical that systemic immunity is not affected, even though the length of the surgical incision is significantly different in the two groups, as the incision probably contributes to a smaller proportion of the induced stress response. This is in contrast to equating a smaller incision with a lower immune stress response.

In patients with a lower baseline T-cell count before operation, laparoscopic surgery was associated with a higher T-cell count on day 3 compared with the open operation. However, this was not seen in patients with a baseline T-cell count greater than 55 per cent (data not shown). While this difference may have arisen by chance as the numbers in this subgroup were small, it is possible that the laparoscopically assisted procedure involves less suppression of the T-cell response when the immune system is not already activated in the patient with colorectal cancer. It is possible that this reduced suppression of T-cell function is not evident in a system that is already maximally stimulated in the presence of malignancy (laboratory reference mean 61·2 per cent, compared with the laparoscopic baseline mean of 63·5 per cent and open baseline mean of 66·1 per cent in *Table 3*).

The absence of any significant difference in the measured parameters does not necessarily imply that an immunological advantage for laparoscopic resection does not exist. Absolute cell number may change without affecting the percentage cell population. Other humoral changes in the complex immune system may certainly alter immune function without altering the peripheral cell counts.

In conclusion, this study did not identify any clinically important difference in T- and B-cell counts, CD4 : CD8 ratio, natural killer cell counts, IgG, IgM and IgA levels, C3 and C4 levels, and the phagocytic activity of white cells between the laparoscopic and open groups. Whether minimally invasive surgery may confer an immune advantage and hence tumour survival advantage requires further investigation. It is clear that, while animal studies may provide an insight into the immunological advantages of laparoscopic resection for colorectal cancer, translation of these findings into the clinical situation requires further appraisal.

Acknowledgements

The authors thank the National Medical Research Council, Singapore, for funding this study, and Ms Carol Loi and Ms Koh Ying Fung of the Polyposis Registry, Department of Colorectal Surgery, Singapore General Hospital, for assisting in data collection.

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Original article

Management of 155 patients with benign liver tumours

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Background: Benign hepatic tumours continue to represent a diagnostic and therapeutic challenge. This study evaluates the indications and results of resection compared with observation in patients with benign hepatic tumours.

Methods: Patients with a primary diagnosis of benign liver tumour were identified from a prospective database and evaluated retrospectively.

Results: From January 1992 to June 1999, 155 patients with benign hepatic tumours were evaluated. The diagnoses included haemangioma (*n* = 97), focal nodular hyperplasia (FNH) (*n* = 42), hepatic adenoma (*n* = 12) and cystadenoma (*n* = 4). Sixty-eight patients (44 per cent) underwent resection because of symptoms (*n* = 36), inability to exclude a malignancy (*n* = 31) or enlargement on serial imaging (*n* = 11). The operative morbidity and mortality rates were 21 per cent and zero respectively. Thirty patients had a preoperative percutaneous needle biopsy, 19 of which were either incorrect or indeterminate. Overall, 39 of 42 patients with symptoms attributed to the tumour were asymptomatic after resection and 18 of 21 patients with symptoms considered unrelated to the tumour were asymptomatic after a period of observation and/or treatment of unrelated conditions (median follow-up 16 months).

Conclusion: When indicated, resection of benign liver tumours can be performed safely. Symptomatic patients with a small FNH or haemangioma can be observed because their symptoms are unlikely to be related to the liver tumour. Percutaneous needle biopsy rarely changes management.

Paper accepted 11 January 2001

British Journal of Surgery 2001, 88, 808–813

Introduction

The diagnosis and treatment of benign liver masses remains controversial. The widespread availability of ultrasonography, computed tomography (CT) and magnetic resonance imaging (MRI), and their frequent application in evaluating abdominal pain, has resulted in more frequent discovery of incidental liver masses. Radiographic distinction between benign and malignant tumours remains a major diagnostic difficulty[1]. Within the category of benign tumours, distinguishing hepatic adenoma from focal nodular hyperplasia (FNH) is important, since treatment will vary, but remains difficult on radiographic grounds[2]. Percutaneous biopsy is often non-diagnostic or misleading[3]. In addition, needle biopsy may be contraindicated, e.g. for hypervascular tumours such as haemangiomas, which may bleed after the procedure[4,5]. There is also a risk of seeding the peritoneal cavity if the lesion is malignant[6,7].

The current indications for surgical management of benign liver masses include uncertain diagnosis with a suspicion of malignancy, severe or progressive symptoms due to size and, less commonly, risk of haemorrhage or rupture. Hepatic adenomas, unlike other benign lesions, have a malignant potential and a significant risk of haemorrhage that is unrelated to size. The decision to resect must be based upon a combination of the radiographic appearance and anatomical position, as well as the surgeon's clinical judgement. However, observation is the optimal management of most patients with benign liver tumours. Laparoscopy has added a new dimension to the treatment, enabling the surgeon to obtain a reliable tissue

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The Editors have satisfied themselves that all authors have contributed significantly to this publication

diagnosis while sparing the patient the morbidity of a laparotomy. In some patients, hepatic cyst fenestrations as well as hepatic tumour resections can be carried out laparoscopically[8–11].

Patients and methods

Between January 1992 and June 1999, a total of 155 patients with benign liver tumours was evaluated. The patient records were reviewed retrospectively. Data collected included the patient's age, sex, symptoms, radiographic findings, results of liver function tests, α-fetoprotein (AFP) and carcinoembryonic antigen (CEA) levels, indications for operation, preoperative diagnosis, surgical procedure, postoperative diagnosis, tumour size, length of hospitalization, postoperative complications and symptoms on follow-up. Preoperative diagnoses included haemangioma, FNH, hepatic adenoma and biliary cystadenoma, based on radiographic appearance. Some patients were referred after a percutaneous needle biopsy. All patients and radiographic studies were presented and discussed at a weekly multidisciplinary hepatobiliary disease management conference.

Additional studies were ordered after the surgeon and at least one radiologist had reviewed the initial films from the referring institution. Patients considered for resection because of symptoms were further investigated to exclude other diagnoses, such as peptic ulcer disease, biliary colic or gastro-oesophageal reflux. Patients suspected of harbouring a primary or secondary hepatic malignancy underwent additional evaluation of the extent of disease as dictated by the suspected diagnosis.

Statistical analysis was performed using a commercially available statistical software package, SPSS 8.0 for Windows (SPSS, Chicago, Illinois, USA). Continuous variables were analysed using the Student's t test, while categorical variables were analysed using χ^2 test.

Results

Most patients were referred after an initial ultrasonographic or CT scan revealed a solitary liver mass of indeterminate origin. *Table 1* summarizes the characteristics of the patients. The mean age was 47 years and 81 per cent were female. Almost half of these patients (49 per cent) were asymptomatic and the mass was found incidentally during investigation of an unrelated condition. After referral, MRI was often used to further evaluate the hepatic lesion, as well as its precise anatomical relationship to the hepatic vasculature. Nuclear medical studies, i.e. tagged red blood cell scan and cholescintigraphy, were not used. Overall, 27

Table 1 Characteristics of all patients with benign liver tumours evaluated from 1992 to 1999

Diagnosis	No. of patients	Mean age (years)	Female	Symptoms	History of cancer	Abnormal liver function tests
Haemangioma	97 (63)	52	73 (75)	48 (49)	17 (18)	5 (5)
FNH	42 (27)	38	38 (91)	18 (43)	9 (21)	5 (11)
Adenoma	12 (8)	34	10 (83)	8 (67)	0 (0)	3 (25)
Cystadenoma	4 (3)	45	4 (100)	2 (50)	1 (25)	2 (50)
Total	155	47	125 (81)	76 (49)	27 (17)	15 (10)

Values in parentheses are percentages. FNH, focal nodular hyperplasia

Table 2 Summary of patients with benign liver tumours submitted to resection

		Indication for operation				
Diagnosis	No. resected	Symptoms	Question of malignancy	Increasing size on serial imaging	Correct preop. diagnosis	Mean hospital stay (days)
Haemangioma	39 (40)*	23	13	8	27	8·5
FNH	18 (43)	8	11	2	7	8·0
Adenoma	8 (67)†	3	6	1	6	8·1
Cystadenoma	3 (75)	2	1	0	2	7·3
Total	68 (44)	36 (53)	31 (46)	11 (16)	42 (62)	8·4

Values in parentheses are percentages. *One with foci of metastatic colorectal carcinoma; †one with a focus of hepatocellular carcinoma. FNH, focal nodular hyperplasia patients (17 per cent) had a history of previously treated cancer. Liver function tests were abnormal in 15 patients (10 per cent); the most common abnormality was a mildly raised alkaline phosphatase level. No patient presented with jaundice. AFP and CEA levels were normal in all but two patients (1 per cent).

Table 2 summarizes the characteristics of 68 patients (44 per cent) who underwent resection. In many patients there was more than one indication for operation. Persistent symptoms and inability to exclude a malignancy were the two most common indications. Overall, the preoperative diagnosis was correct in 62 per cent of patients. The mean duration of hospitalization was 8·4 days. In two operative cases, a focus of malignancy was found within an otherwise benign tumour. One of these patients had a history of previously resected colon cancer and the resected hepatic mass contained a focus of metastatic disease within a haemangioma. A second patient had a focus of hepatocellular carcinoma contained completely within an adenoma.

The operations performed and tumour sizes are described in *Table 3*. Thirty-three liver tumours (49 per cent), mostly haemangiomas, were enucleated, while the remainder were excised by anatomical resection. The mean tumour size was 10·4 cm. There were a total of 14 postoperative complications (21 per cent) and no postoperative deaths. Infectious complications occurred in five patients, another five patients had sterile fluid collections requiring percutaneous drainage, two patients developed a pneumothorax and one patient required reoperation for bleeding.

At a median follow-up of 16 months, 39 of 42 patients who were symptomatic before operation had resolution of the symptoms after resection. Resection relieved symptoms in 21 of 23 patients with haemangioma and all patients with FNH. Two patients had persistent pain after resection of a haemangioma and one after resection of an adenoma. Eighteen of 21 patients managed non-operatively are currently asymptomatic at follow-up, while three remain symptomatic. One of these patients had an 8-cm haemangioma and is being considered for resection while two others have small haemangiomas that are unlikely to be the cause of the symptoms.

The relationship between tumour size and presence of symptoms on initial presentation was analysed for the subset of patients with FNH and haemangioma, the two most frequent diagnoses. Patients with FNH who were symptomatic had a mean(s.d.) tumour size of 7·3(6·6) cm, while those without symptoms had a mean tumour size of 4·4(2·1) cm (P = 0.06). The mean tumour size in symptomatic and asymptomatic patients with haemangioma was 10·0(8·0) and 6·8(5·8) cm respectively (P = 0·03). When FNH and haemangioma were analysed together, the mean tumour size in symptomatic and asymptomatic patients was 9·2(7·6) and 6·0(5·0) cm respectively (P = 0·003). Twenty-one of 31 patients with tumours larger than 10 cm were symptomatic. By contrast, only 38 of 95 patients with tumours smaller than 10 cm had symptoms attributed to the tumour (χ^2 = 7·2, 2 d.f., P = 0·007).

In patients subjected to percutaneous needle biopsy, the biopsy results were compared with the final histopathological or radiographic diagnoses. The final radiographic diagnosis was used as the basis for comparison in patients managed non-operatively and followed over a prolonged period (n = 19), while the final pathological diagnosis was used as the basis for comparison in patients who underwent operation (n = 11). The percutaneous biopsy correlated with the final diagnosis in only 11 of the 30 patients subjected to this procedure. The majority of the biopsies were either indeterminate or showed normal hepatocytes.

Discussion

Benign liver tumours continue to present diagnostic and therapeutic challenges. They are frequently an incidental finding during assessment of unrelated conditions, or in the staging of patients with malignancy. The results of this analysis of 155 patients with benign liver tumours treated over a 7-year period show that many of these patients can be

Table 3 Operative procedures performed in patients with benign liver tumours

Diagnosis	Enucleation	Segmentectomy	Lobectomy	Trisegmentectomy	Tumour size (cm)*
Haemangioma	21	8	6	4	12·1 (3–30)
FNH	7	3	6	2	7·1 (2–30)
Adenoma	4	1	2	1	8·6 (3–21)
Cystadenoma	1	0	0	2	13·0 (10–16)
Total	33	12	14	9	10·4 (2–30)

*Values are mean (range). FNH, focal nodular hyperplasia observed safely. Resection was reserved for symptomatic patients, those with premalignant conditions and those in whom it was not possible to exclude other possible diagnoses. Resection led to symptom resolution in 39 of 42 patients with symptoms. Symptoms thought to be inconsistent with the hepatic tumour resolved without the need for operation in 18 of 21 patients. In particular, patients with small lesions were less likely to have associated symptoms and may benefit from a period of observation. Hepatic adenoma and cystadenoma should always be considered for resection because of possible malignant degeneration (as well as spontaneous haemorrhage in the case of adenoma). Diagnostic uncertainty accounted for operation in 31 of 68 resected patients. Of the 11 misidentified FNH lesions, six were thought to be adenomas, while the remainder were diagnosed as either well differentiated hepatocellular carcinoma or another malignancy. The preoperative diagnosis of FNH was correct in only seven of 18 resected patients. Haemangiomas were less likely to cause diagnostic uncertainty, but eight of 39 of these lesions were thought to represent either a primary or secondary malignancy before operation. It should be emphasized that the haemangiomas that were confused for other lesions were smaller or sclerosed, making them difficult to distinguish from malignant tumours.

To improve diagnosis, percutaneous needle biopsy and MRI were utilized. Biopsy carries the risk of bleeding and tumour dissemination, often yields inadequate or erroneous information, and does not preclude the possibility of a malignancy when normal tissue is found. Only 11 of 30 biopsies were accurate in the current study. MRI is rapidly

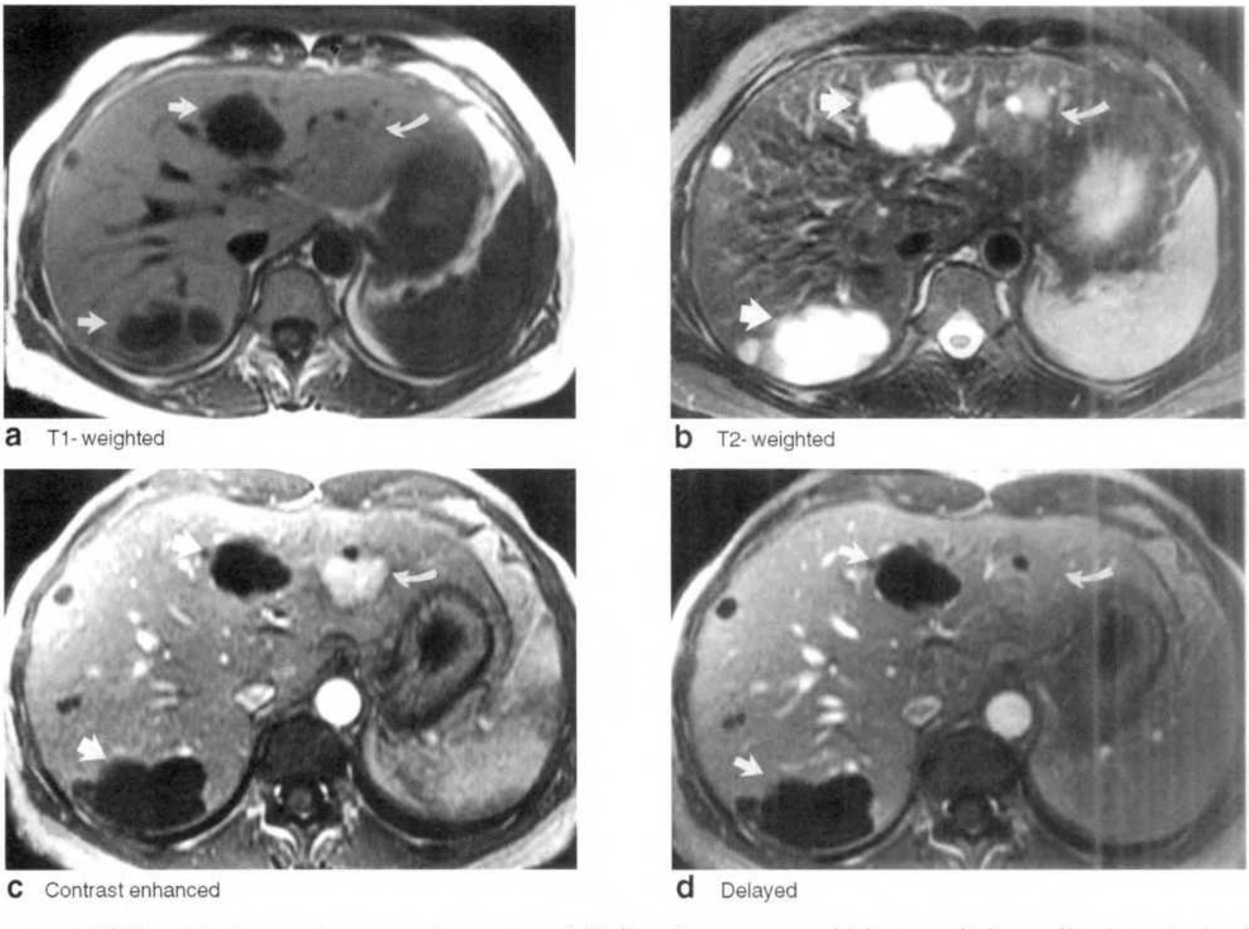
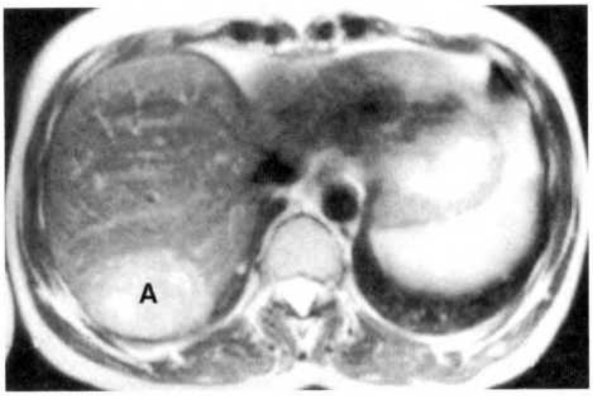
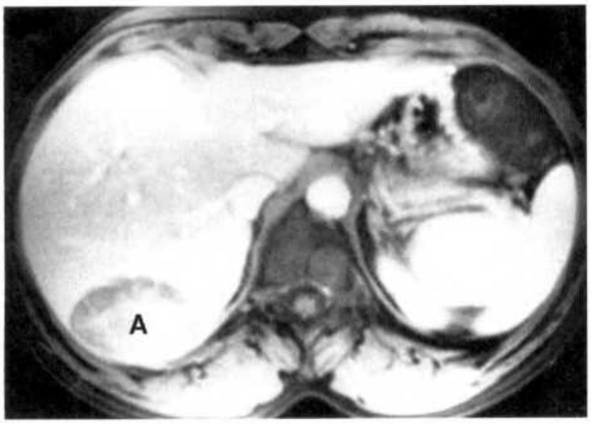


Fig. 1 **a** Axial T1-weighted magnetic resonance image through the liver demonstrates multiple cysts, which are of low intensity signal (arrows) and an area of isointensity, which is focal nodular hyperplasia (FNH) (curved arrow). **b** On the T2-weighted image, the cysts appear bright (arrows) and the area of FNH is isointense to slightly hyperintense (curved arrow). Note that this area of FNH is associated with a tiny cyst. **c** After administration of contrast, the cysts do not enhance (arrows), while the area of FNH enhances intensely and homogeneously (curved arrow). **d** On delayed images, the cysts again do not enhance (arrows), while the area of FNH is isointense to the hepatic parenchyma (curved arrow)

evolving and is a vital tool for characterizing benign liver tumours. While the present study was not designed to analyse the predictive value of MRI, a recent analysis showed that MRI provided accurate diagnostic information in 95 of 96 problematic benign liver lesions[12]. Gadolinium-enhanced MRI is useful for differentiating haemangiomas from malignancies[13,14]. MRI is virtually diagnostic in simple hepatic cysts and haemangiomas. However, distinguishing FNH from hepatic adenoma may not always be possible. FNH is isointense on T1-weighted images and slightly hyperintense on T2. It enhances intensely with gadolinium and then becomes isointense to liver on delayed images (*Fig. 1*). In contrast, hepatic adenoma is hyperintense on T2-weighted images and enhances heterogeneously following contrast administration (*Fig. 2*).



a T2-weighted



b Contrast enhanced

Fig. 2 **a** The T2-weighted magnetic resonance image of an adenoma in the posterior right hepatic lobe (A) is moderately hyperintense with focal areas of hyperintensity. **b** The adenoma enhances heterogeneously on axial images after contrast administration

In general, patients with asymptomatic FNH or haemangioma should be observed. Two large published series support this approach. Weimann *et al.*[15] reviewed their experience with 437 patients with benign liver tumours, including 238 patients with haemangioma. Asymptomatic patients with an unequivocal diagnosis of haemangioma or FNH were observed. No patient proved to have a malignancy or experienced tumour rupture. Overall, unresected haemangiomas are usually asymptomatic and rarely increase in size[16]. Hepatic artery embolization, which has been used in the emergency treatment of acute haemorrhage from ruptured hepatic adenomas and hepatocellular carcinomas[17,18], can be used to treat hepatic adenomas in patients who are not candidates for resection. Shrinkage in tumour size after embolization may be followed by resection in selected patients. Asymptomatic adenomas should be observed only if their size decreases on serial imaging studies, which may occur after cessation of hormone therapy. Patients with solid lesions that are

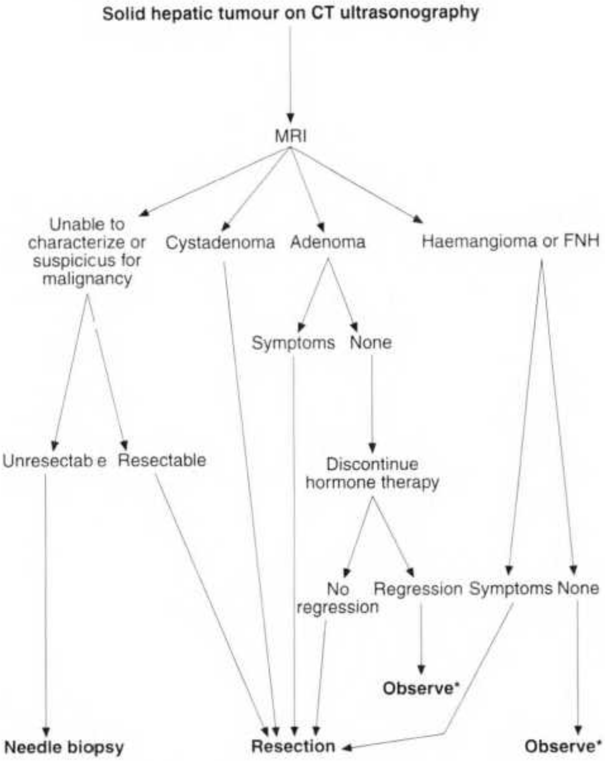


Fig. 3 Algorithm for management of benign liver tumours. If a resectable lesion is suspicious for a malignancy then staging, including evaluation for an extrahepatic primary lesion, should precede resection. *Increasing size on serial radiographic imaging during observation is an indication for resection. CT, computed tomography; MRI, magnetic resonance imaging; FNH, focal nodular hyperplasia

difficult to characterize on MRI or suspicious for malignancy should either undergo resection or a needle biopsy if unresectable. For any tumour being observed, increasing size on serial imaging is an indication for resection.

Surgical options for a solid benign liver tumour include enucleation and anatomical resection, depending on the location and size of the lesion. Particularly for haemangiomas, enucleation has been reported to reduce operative blood loss when compared with anatomical resection owing to the presence of an outer rim of fibrous tissue and compressed liver, which allows for simple dissection[19]. This technique was associated with fewer intra-abdominal complications than anatomical resection in a recent case–control study[20]. In the present series, 33 (49 per cent) of 68 benign solid liver tumours were enucleated.

An algorithm for the diagnosis and treatment of benign liver tumours is shown in *Fig. 3*. Ultrasonography and CT are typically used to identify the benign tumour. MRI is used to further characterize the mass. While simple cysts are considered benign lesions, biliary cystadenomas are true neoplasms which cannot only produce abdominal symptoms, but also undergo malignant degeneration. These lesions are generally thick walled and form internal septations.

In summary, the management of benign liver lesions depends primarily on the clinical presentation and the radiographic appearance. MRI may be helpful when the diagnosis is dubious while percutaneous biopsy is generally avoided. Overall, most patients can be safely observed. The indications for operation are persistent symptoms suspected to be due to the tumour, a chance of malignant transformation or rupture, or inability to exclude a malignancy. Resection can be performed with acceptable morbidity and mortality rates. Asymptomatic patients with benign hepatic tumours that are stable in size can be followed safely with serial radiographic imaging and ultimately discharged from follow-up.

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Short note

Botulinum toxin injection is an effective treatment for axillary hyperhidrosis

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Paper accepted 7 January 2001

Introduction

Excessive axillary sweating causes profound embarrassment and social disability, with stained and damaged clothing. Patients often seek surgical treatment as a last resort. Thoracoscopic sympathetic denervation of the axillary skin requires ablation of at least the T2 and T3 ganglia, with an incidence of compensatory hyperhidrosis that is unacceptable to most patients with hyperhidrosis confined to the axilla. This study examined the use and effectiveness of *Clostridium botulinum* type A toxin in patients with isolated axillary hyperhidrosis.

Patients and methods

Sixteen patients (eight women) with predominantly axillary hyperhidrosis were injected at 12 equally spaced points in each axilla with Dysport® (Ipsen, Maidenhead, UK) (0·1-ml aliquots, each containing 20 mouse units) using a 25-G needle. The area for injection typically corresponded to the elliptical hair-bearing area.

Ten patients had quantitative assessment of axillary sweating over 1 h immediately before and several months after injection of toxin, using weighed gauze swabs. Ten patients underwent a repeat set of injections after 1 year.

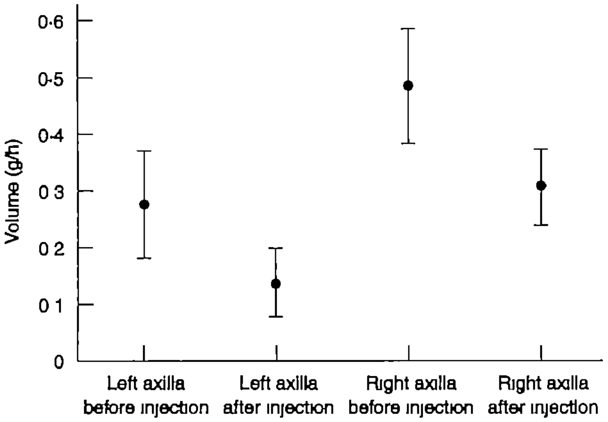

Fig. 1 Volume of sweat collected in 1 h on gauze swabs held in the axilla before and after injection of botulinum A toxin in ten patients (1 g of sweat is equivalent to 1 ml)

Results

There were no complications at or around the time of treatment. All patients reported complete dryness of both axillae within 3 days of injection (40 per cent within 24 h). Patients were very satisfied with the results, with particular reference being made to the freedom to wear any clothing and increased social confidence.

The mean(s.e.m.) duration of action of the toxin was 9(1) (range 5–13) months, with a gradual return of sweating in all but one patient. Three patients experienced a single episode of sudden breakthrough sweating, with a return to dryness thereafter, one at 8 months and two at 3 months. Ten patients underwent repeat injections after 1 year, with good effect.

Sweat volume measurements showed a mean decrease after injection of botulinum A toxin (*Fig. 1*).

Discussion

This study has shown that intradermal injection of botulinum A toxin is a highly effective and well tolerated treatment for isolated axillary hyperhidrosis. The toxin acts to disrupt vesicular release in the cholinergic sympathetic nerve terminals. Function is regained as new terminals and synapses grow[1]. The phenomenon of breakthrough sweating occurring spontaneously several months after treatment has not, to the authors' knowledge, been reported previously. A similar phenomenon has been seen in patients who have had thoracoscopic sympathectomy in this unit.

Assessment of efficacy with this procedure is subjective. The measurements with gauze showed a small decrease in sweat volume, but the errors due to small sample size were large, exemplified by the difference between each side. Other researchers have used different techniques over short periods, but these are also likely to be inaccurate[2].

This technique is not used for the treatment of palmar hyperhidrosis; intrinsic muscle weakness has been documented in up to 25 per cent of patients[3]. Antibodies may develop and reduce the efficacy of repeat injections in a small proportion of patients[4].

Further studies are needed to determine dose–response data to botulinum toxin. The doses are not comparable with those of the other commercial product, Botox® (Allergan Pharmaceuticals, Irvine, California, USA), which has a potency approximately 2.5–4-fold greater than that of Dysport®[5].

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Original article

Microcirculatory effects of experimental acute limb ischaemia–reperfusion

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Background: The object of this study was to develop an animal model in which changes in microvascular haemodynamics and leucocyte–vessel wall interactions due to acute limb ischaemia–reperfusion (I/R) can be measured in the skin. Furthermore, it was investigated whether these changes are related to local muscle injury.

Methods: Male Lewis rats were subjected to unilateral limb ischaemia for 1 h ($n = 8$) or 2 h ($n = 8$) by cuff inflation, or to a sham protocol ($n = 6$). Intravital video microscopic measurements of leucocyte–vessel wall interactions, venular diameter, red blood cell velocity and reduced velocity (which is proportional to wall shear rate) were performed in skin venules before ischaemia and at 0·5, 1, 2, 3 and 4 h after the start of reperfusion. Oedema and leucocyte infiltration of ischaemic/reperfused skeletal muscle were quantified histologically.

Results: In skin venules, both 1 and 2 h of ischaemia induced a significant increase in leucocyte rolling (six and five times baseline, respectively; $P < 0·05$) and adherence during reperfusion (eight and four times baseline; $P < 0·05$). No significant increase in muscular leucocyte infiltration was detected. After an initial hyperaemic response of 180 per cent of baseline values ($P < 0·05$), blood flow decreased to about 60 per cent after 4 h of reperfusion in skin venules of both experimental groups. I/R induced tibial muscle oedema, the severity of which depended on the ischaemic interval (wet to dry ratio: control, 4·0; 1 h, 4·5 (P not significant); 2 h, 5·8 ($P < 0·05$)).

Conclusion: A non-invasive animal model was developed that enables investigation of the consequences of acute limb I/R.

Paper accepted 11 February 2001

British Journal of Surgery 2001, 88, 816–824

Introduction

Prevention and treatment of acute limb ischaemia–reperfusion (I/R) injury remains an important challenge in vascular surgery. Revascularization of a limb after a prolonged period of acute-onset ischaemia is associated with high rates of mortality (10–20 per cent) and morbidity (20–30 per cent)[1–4]. This revascularization syndrome may lead to several complications, both local (compartment syndrome, rhabdomyolysis) and systemic (adult respiratory distress syndrome, multiple organ failure).

Several mechanisms are involved in the development of I/R injury. There is increasing evidence that endothelial cell function is compromised in all regions of the microvasculature in tissues exposed to ischaemia and reperfusion[5]. The venular endothelial cells appear to be most affected, as reflected by an enhanced production of reactive oxygen metabolites and an increased expression of adhesion molecules that are involved in leucocyte–vessel wall interactions[5]. The effectiveness of antineutrophil serum, monoclonal antibodies directed against several adhesion molecules involved in leucocyte–vessel wall interactions, and of free radical scavengers in the treatment of I/R injury corroborate the involvement of leucocyte–vessel wall interactions and reactive oxygen metabolites[6–8].

Despite recent therapeutic advances that reduce the extent of I/R injury, it would be even better to prevent the development of the revascularization syndrome. The latter requires further insight into the underlying mechanisms. For this purpose a suitable animal model is of importance.

Hardy *et al.*[9] developed a model in which ischaemia in the rat hind limb was induced using a tourniquet. They quantified skeletal muscle blood flow using radioactive microspheres, but they did not investigate local leucocyte–vessel wall interactions. Other animal models of acute limb ischaemia described previously require extensive surgical manipulation either to induce ischaemia or to visualize leucocyte–vessel wall interactions by means of intravital microscopy[10–13]. To avoid changes in local haemodynamics and the induction of an inflammatory response[14,15], the ideal model would not require a traumatizing technique at all.

Recently, a rat model has been developed in which leucocyte–vessel wall interactions and microvascular haemodynamics can be studied in the skin of a hind paw without the need for any surgical procedure[16,17]. This was used to investigate whether non-surgically-induced acute hind limb ischaemia followed by reperfusion leads to microcirculatory changes in the skin of the rat hind paw. In addition, it was investigated whether these changes could be related to local muscle injury.

Materials and methods

Animals and anaesthesia

All experiments were approved by the Institutional Animal Care Committee. In total, 22 male Lewis rats, with a mean weight of 311 (range 280–325) g, were obtained from the animal facility of Maastricht University. Sodium pentobarbital (Narcovet®; Amarpho, Arnhem, The Netherlands) was injected intraperitoneally (60 mg per kg body-weight) to induce anaesthesia, under a short sedation by carbon dioxide (40 per cent carbon dioxide in air). Administration of pentobarbital was repeated whenever necessary (20 mg per kg body-weight intravenously via the tail vein). Throughout each experiment, body core temperature was maintained at 37°C, using an infrared heating lamp controlled by a thermoanalyser connected to a rectal probe. Blood pressure and heart rate (HR) were measured at 15-min intervals using a non-invasive tail programmed electrosphygmomanometer (model PE-300; Narco Biosystems™, Houston, Texas, USA).

Intravital video microscopy

An intravital microscope (Leitz™, Wetzlar, Germany), adapted to telescopic imaging[18], was used to visualize the most superficial blood vessels in the skin of a toe. The microscope was equipped with a Leitz Ploem-opak, carrying a Pol-cube, and an L20 objective (numerical aperture 0·32), yielding a final optical magnification at the front plane of the charge coupled device (CCD) camera (Hamamatsu CCD, camera type C3077-01, Hamamatsu Photonics, Hamamatsu City, Japan) of 25 ×. Observations were performed under bright field epi-illumination with a xenon lamp (150 W). Microscopic images were recorded on videotape (Supervise; Sony™, Tokyo, Japan).

All microscopic observations were performed on the lateral or medial side of the third toe of the left and right hind paw respectively. To prevent motion artefacts, the hind paw under investigation was fixed on the microscope stage with plastic clay. The area of skin used for observation was covered with a thin layer of paraffin oil to diminish surface reflections. In each paw, one postcapillary venule was observed with a mean diameter of 15 (range 8–24) μm. The midplane of the selected vessel (i.e. its largest diameter) was kept in focus. To ascertain visualization of all rolling and adhering leucocytes, the objective lens was focused up and down through the lumen in some of the greater venules. In this way it could be assured that leucocytes rolling along the lower and upper vessel wall were always seen when the point of focus was in the midplane of the vessel.

Experimental protocol

Experiments were performed in three groups; no ischaemia was induced during the 6-h protocol in the control group ($n = 6$), whereas in the other two groups unilateral limb ischaemia was induced for 1 h ($n = 8$) or 2 h ($n = 8$), followed by a reperfusion interval of 4 h.

In both the ischaemic and the contralateral hind paw, the selected venule was recorded for at least 5 min at the beginning of an experiment to enable assessment of baseline fluid dynamic conditions and leucocyte rolling and adhesion levels. Immediately thereafter, unilateral ischaemia was induced: the blood supply to the left hind limb was stopped by inflating a cuff around the rat's thigh to a pressure of 300 mmHg. In addition, a rubber tourniquet was put as high as possible around the same hind limb to keep the cuff in position. Total limb ischaemia was verified by the intravital microscopic observation that blood flow had stopped completely in the microvessels of the skin of the ischaemic hind paw. Just before deflation of the cuff, as well as 30, 60, 120, 180 and 240 min after start of reperfusion of the ischaemic hind limb, the selected venules in both limbs were again recorded for 5 min each. At the end of the last observation, the animals were killed using an overdose of sodium pentobarbital.

Data analysis

All experiments were analysed off-line from videotape. The incidence of leucocyte rolling and adhesion was determined. All leucocytes that could be seen moving by eye were considered to be rolling. Individual, free-flowing leucocytes move with the velocity of the blood flow and therefore cannot be detected by eye. Rolling leucocytes move at least an order of magnitude slower and consequently are easy to detect. The degree of leucocyte rolling in each observed venule was quantified by counting the number of leucocytes passing through a cross-section of the vessel and was expressed as the number of cells passing per minute. Leucocytes were considered to be adherent when they remained stationary for 30 s or longer. The number of adherent leucocytes was determined in a 100-µm vessel segment.

Mean red blood cell velocity (V_{RBC}) was determined using a temporal correlation method incorporated in the automated Capiflow software (Capiflow™, Krista, Sweden)[19]. Vessel diameters were measured using a custom-built image-shearing device[20]. The blood flow (Q) through a vessel was calculated by means of the following equation:

$$Q = V_{RBC} \times \Pi\left(\frac{D_v}{2}\right)^2$$

where D_v is the vessel diameter. Reduced velocity (U), which is proportional to wall shear rate, was calculated according to the equation:

$$U = \frac{V_{RBC}}{D_v}$$

Systemic leucocyte counts

At the end of the experiment, after 4 h of reperfusion, an arterial blood sample was withdrawn from the abdominal aorta to assess the number of circulating monomorphonuclear and polymorphonuclear leucocytes. A mixture of 20 µl of arterial blood and 180 µl of Türks solvent (1 per cent acetic acid, 1 per cent methylviolet) was examined by light microscopy in a counting chamber (Clay Adams™, Pansippany, New Jersey, USA).

Wet to dry ratios and histology

To determine the extent of I/R-induced oedema, biopsies were taken from the mid-portion of the posterior tibial muscles of both hind paws, immediately after death. Wet to dry ratios were obtained by weighing before and after freeze-drying overnight.

In addition, biopsies from the same muscles were fixed in 10 per cent phosphate-buffered formaldehyde and embedded in paraffin. Transverse 4-µm sections were cut, stained with haematoxylin and eosin, and examined by light microscopy. For each section, five fields of view were scored by two observers using a grid. The total number of myocytes in the screen as well as the number of round (oedematous) myocytes and leucocytes were counted. This semiquantitative scoring system was used to determine the extent of tissue damage, characterized by oedema and accumulation of leucocytes.

Statistical analysis

The SPSS-PC+ package (SPSS®, Chicago, Illinois, USA) was used. Because of their non-symmetrical distribution, most data are presented as median (interquartile range (i.q.r.)). To enable comparisons between groups, some data were normalized to baseline values. The non-parametric Mann–Whitney *U* test was used to test for significant differences between groups. For analysis of differences over time within the same group, the paired Wilcoxon signed rank test was used. The Spearman rank correlation test was used to test correlations between two groups of data. Differences were considered statistically significant when $P < 0.05$.

Results

All rats survived the whole experimental protocol. Inflation of the cuff positioned around the left thigh resulted in complete ischaemia of the hind limb, as verified microscopically by cessation of flow in all skin microvessels examined.

Systemic haemodynamics

During baseline measurements, mean (range) mean arterial pressure (MAP) was 104 (95–120) mmHg and mean HR was 365 (300–450) beats per min (all groups pooled). There were no initial differences in MAP or HR between the groups. Throughout the experiments, MAP and HR remained constant in all groups (data not shown).

Leucocyte–vessel wall interactions

At baseline the overall median (i.q.r) number of rolling leucocytes was 2 (0–4) per min, whereas almost no adhering leucocytes were present (0 (0–1) per 100 µm). There were no significant differences between the three groups or between the two hind limbs (ischaemic and contralateral). In the control group, no significant change in leucocyte rolling was observed over time.

The effect of 1 and 2 h of ischaemia and subsequent reperfusion on leucocyte rolling is illustrated in *Fig. 1*. One hour of ischaemia induced a significant increase in leucocyte rolling during the whole reperfusion period

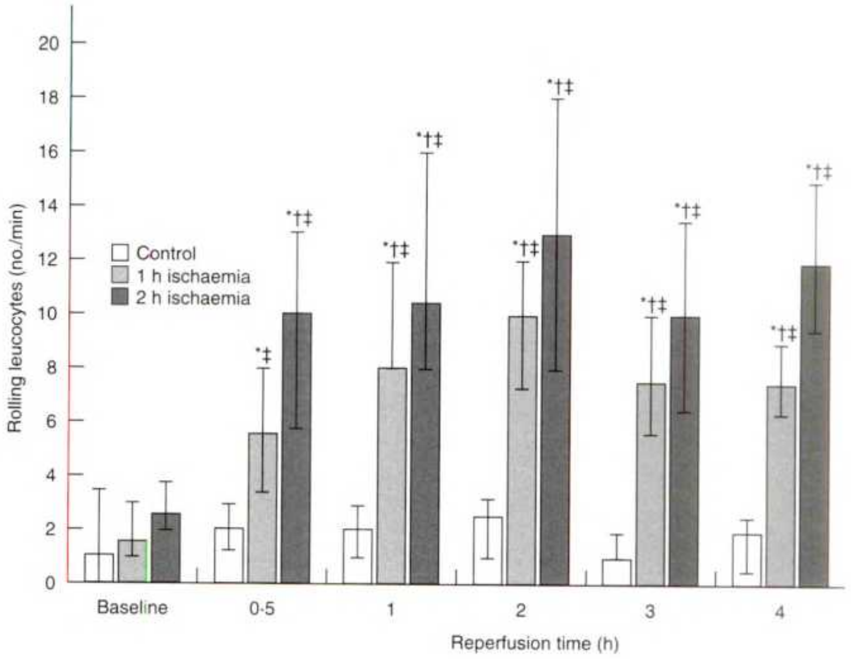

Fig. 1 Effects of ischaemia followed by reperfusion on the absolute number of rolling leucocytes in the experimental left hind limb. Data are expressed as median (interquartile range). $^*P < 0{\cdot}05$ *versus* baseline (Wilcoxon signed rank test); $^\dagger P < 0{\cdot}05$, ischaemic *versus* contralateral limb; $^\ddagger P < 0{\cdot}05$ *versus* control group (Mann–Whitney U test)

Table 1 Baseline values of local haemodynamic variables

	Limb	Control	1 h ischaemia	2 h ischaemia
D_v (µm)	Experimental	15 (10–21)	14 (10–19)	13 (8–20)
	Contralateral	15 (9–24)	18 (15–19)	13 (9–18)
V_{RBC} (mm/s)	Experimental	0·4 (0·2–0·5)	0·4 (0·2–0·6)	0·4 (0·2–0·6)
	Contralateral	0·3 (0·1–0·4)	0·3 (0·2–0·5)	0·3 (0·2–0·5)
Q (× 10^4 µm^3/s)	Experimental	7·2 (1·8–17·8)	6·2 (2·8–15·7)	5·3 (2·1–10·8)
	Contralateral	5·2 (1·6–11·2)	8·0 (3·8–13·5)	4·8 (1·3–10·3)
U (per s)	Experimental	25 (11–41)	27 (19–37)	30 (11–51)
	Contralateral	20 (7–35)	19 (9–32)	26 (10–50)

Values are median (interquartile range). D_v, diameter of the observed venule; V_{RBC}, red blood cell velocity; Q, flow; U, reduced velocity

($P < 0{\cdot}05$); this increase was already present at 30 min and peaked at 2 h after the start of reperfusion. Two hours of ischaemia had a similar effect: the level of leucocyte rolling increased significantly, with a maximum after 2 h of reperfusion ($P < 0{\cdot}05$). No differences were found between these two groups. In the contralateral, right hind limb no significant change in leucocyte rolling was observed over time in any of the groups.

Fig. 2 shows the effect of 1 and 2 h of ischaemia and subsequent reperfusion on the number of adherent leucocytes. In the control group, virtually no adherent leucocytes and no time-dependent changes were observed. Following 1 or 2 h of ischaemia, however, a significant increase in leucocyte adhesion was observed during reperfusion with the highest values observed after 4 h of reperfusion ($P < 0{\cdot}05$). No changes in the number of adhering leucocytes were observed over time in the contralateral hind limb (data not shown).

Local haemodynamics

No differences in baseline values of the local haemodynamic variables were observed between the three groups (*Table 1*). During the experiments, venular diameters remained constant in both the control group and the group subjected to ischaemia for 1 h (data not shown). In the experimental

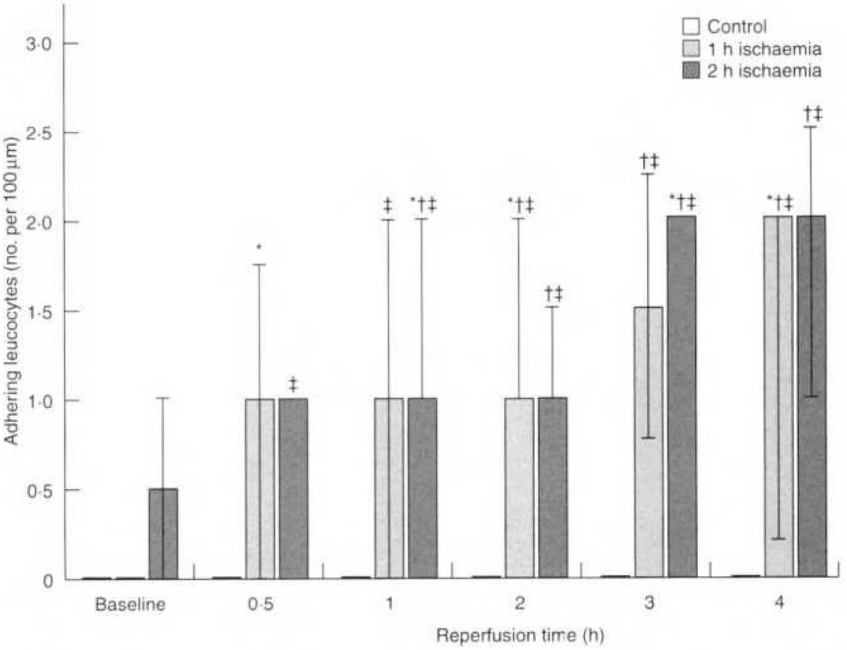

Fig. 2 Effects of ischaemia followed by reperfusion on the number of adherent leucocytes in the experimental left hind limb. Data are expressed as median (interquartile range). $^*P < 0{\cdot}05$ *versus* baseline (Wilcoxon signed rank test); $^\dagger P < 0{\cdot}05$, ischaemic *versus* contralateral limb; $^\ddagger P < 0{\cdot}05$ *versus* control group (Mann–Whitney *U* test)

limb of the 2-h ischaemia group a transient increase in venular diameter of 27 and 12 per cent was observed after 0·5 and 1 h of reperfusion respectively ($P < 0{\cdot}05$ *versus* baseline values and the contralateral limb).

No significant change in V_{RBC} was seen in either limb of the control group. In both experimental groups, no change in V_{RBC} was observed in the contralateral hind limb. In the ischaemic hind limb of the 1-h ischaemia group, however, V_{RBC} increased significantly to about 130 per cent of baseline values after reperfusion for 30 min ($P < 0{\cdot}05$). Subsequently, V_{RBC} normalized to baseline values, and even tended to decrease after 4 h of reperfusion (59 per cent of baseline values; $P = 0{\cdot}21$). In the 2-h ischaemia group V_{RBC} increased non-significantly to 122 per cent of baseline values after reperfusion for 30 min; subsequently, it decreased significantly to 54 per cent of baseline values ($P < 0{\cdot}05$) after reperfusion for 4 h.

The changes in venular blood flow showed a similar trend (*Fig. 3*). Blood flow remained constant in both limbs of the control group and in the contralateral limbs of the experimental groups. However, in the ischaemic hind limbs of the experimental groups, blood flow increased significantly within 30 min of reperfusion (to 182 per cent and 179 per cent of baseline values respectively; $P < 0{\cdot}05$ in both groups). After this hyperaemic phase, blood flow normalized to baseline values and decreased further during the second half of the reperfusion phase to 64 and 56 per cent of baseline values in animals subjected to ischaemia for 1 and 2 h respectively ($P = 0{\cdot}06$ and $P = 0{\cdot}05$).

Reduced velocity, which is a measure of wall shear rate, remained constant in the control and 1-h ischaemia group (data not shown). In the 2-h ischaemia group, however, a significant ongoing decrease in reduced velocity was observed in the ischaemic limb after 1 h reperfusion (73 per cent of baseline values; $P < 0{\cdot}05$), to 49 per cent of baseline values after 4 h ($P < 0{\cdot}05$).

Systemic leucocyte count

To exclude the possibility that the observed increase in rolling and adhering leucocytes in the experimental groups was due to changes in the number of circulating monomorphonuclear and polymorphonuclear leucocytes, the total number of systemic leucocytes, as well as their differentiation, were analysed. No significant differences were found between the two experimental groups and the control group with respect to the total number of systemic leucocytes in the arterial blood samples after 4 h of reperfusion (median (i.q.r) 31 (28–35) $\times 10^6$, 26 (24–29) $\times 10^6$ and 40 (31–43) $\times 10^6$ cells/ml in the control, 1-h ischaemia and 2-h ischaemia groups respectively; $P > 0{\cdot}05$), and the percentage of polymorphonuclear leucocytes (19, 19 and 12 per cent respectively; $P > 0{\cdot}05$).

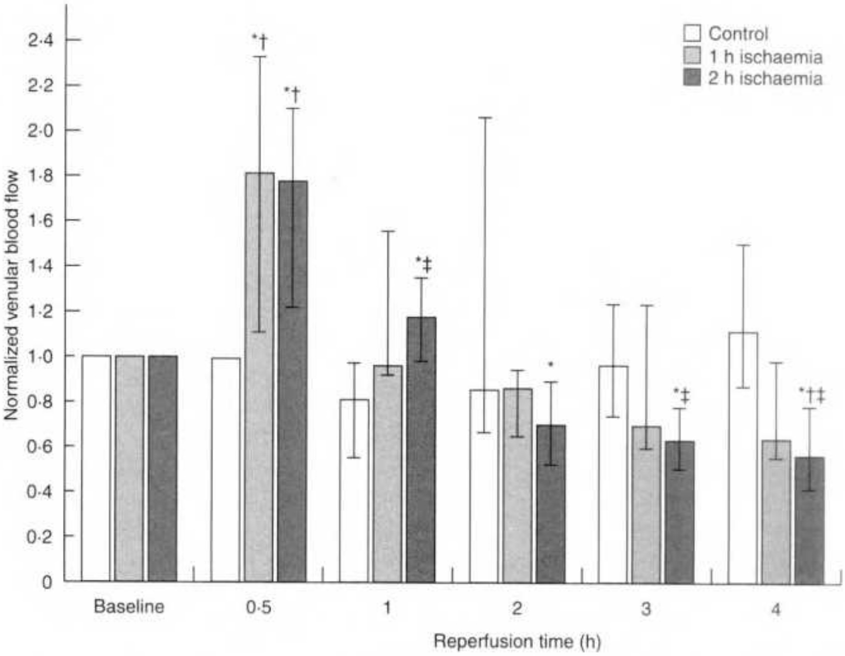

Fig. 3 Effect of ischaemia followed by reperfusion on venular blood flow in the experimental left hind limb. Data are expressed as median (interquartile range) and normalized to preischaemic values. *P < 0·05 *versus* baseline (Wilcoxon signed rank test); †P < 0·05, ischaemic *versus* contralateral limb; ‡P < 0·05 *versus* control group (Mann–Whitney U test)

Histology and wet to dry ratios of hind limb muscle

The wet to dry ratios of tibial muscle biopsies of the ischaemic hind paw in the 1-h ischaemia and control groups were similar (4·5 and 4·0 respectively) but that in the 2-h ischaemia group (5·8) was significantly higher than that in the control group (P < 0·05).

The number of round (i.e. oedematous) muscle cells, expressed as a mean percentage of the total number of cells, in the ischaemic hind limbs of both experimental groups (1-h ischaemia: 58 (range 1–98) per cent, P < 0·01; 2-h ischaemia: 77 (47–100) per cent, P < 0·001) was significantly higher than in the control group (0 (0–0) per cent). No change was seen in the contralateral limb in both experimental groups.

Consistent with the relatively small increase in the number of adhering leucocytes in the skin venules, no significant differences in the mean number of infiltrated leucocytes in tissue sections of tibial muscle biopsies between the experimental and contralateral limbs were seen within the three groups, or between the three groups (control: 0 (range 0–0) and 0·4 (0–1·3) per mm^2; 1-h ischaemia: 0·2 (0–0·4) and 0·1 (0–0·4) per mm^2; 2-h ischaemia: 1·0 (0·2–2·9) and 0 (0–0) mm^{-2}).

Fig. 4 illustrates the relationship between the number of adhering leucocytes in skin venules and the level of leucocyte infiltration in tibial muscle following I/R in the ischaemic hind limb. A significant relationship was found between these variables (r_S = 0·679, P < 0·01).

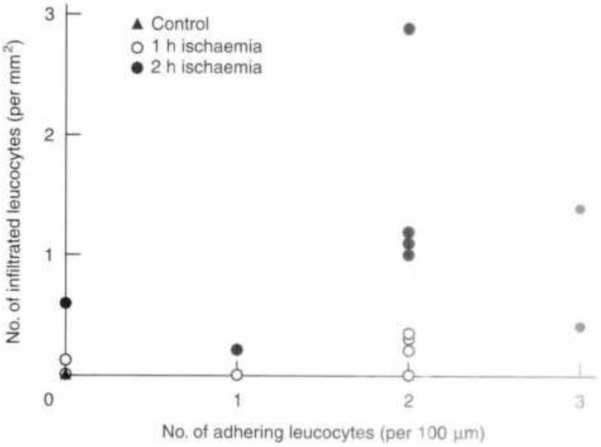

Fig. 4 Relation between the number of adhering leucocytes in skin venules and the level of leucocyte infiltration in tibial muscle following ischaemia–reperfusion injury in the ischaemic hind limb. Individual data points after 4 h of reperfusion are shown (control group, n = 6; 1 h ischaemia, n = 7; 2 h ischaemia, n = 8). r_S = 0·679, P < 0·01

Discussion

This article presents a new model of acute hind limb I/R in which ischaemia is induced without the use of surgery. The model allows investigation of the microvascular consequences of I/R in the skin without traumatizing the tissue and allows visualization of leucocyte–vessel wall interactions in postcapillary venules, without using fluorescent labelling dyes.

Temporary total occlusion of the rat hind paw circulation, by means of cuff inflation, followed by reperfusion induces an increase in leucocyte–vessel wall interactions in skin postcapillary venules as early as 30 min after the start of reperfusion. An increase in leucocyte–vessel wall interactions is generally believed to be an early sign of an initiating inflammatory response[21]. An increase in the expression of leucocyte adhesion molecules such as P- and E-selectin on the endothelial cell membrane enables such leucocyte–vessel wall interactions[22–24]. The progression of this inflammatory response over time, with the loose and reversible leucocyte–endothelium interactions (i.e. rolling) peaking around 2 h after the start of reperfusion and the more permanent interactions (i.e. adherence) steadily increasing up to 4 h after reperfusion, is in line with the observations from several other studies[25,26]. Adhesion of leucocytes to the vascular endothelium requires expression of integrins and members of the immunoglobulin superfamily, which is known to take several hours after the initial triggering event[27,28].

In this model, there was no histological evidence of leucocyte infiltration into the hind limb muscular tissue. This is not necessarily in contradiction with the marginal increase in leucocyte adhesion levels seen after ischaemia and 4 h reperfusion. Using comparable models, other reports suggest that reperfusion for at least 5–24 h is required before any overt infiltration can be detected histologically[29,30]. Nevertheless, this model does reveal histological evidence of early soft tissue damage, as indicated by oedematous swelling of myocytes and the increased wet to dry ratio, which is in agreement with other reports[31,32].

In both I/R groups there was a temporal reactive hyperaemia as measured by significant increases in skin venular blood flow. In a similar model, Hardy *et al.*[9] observed a temporal decrease in muscle perfusion at 10 min of reperfusion following 2 h of unilateral hind limb ischaemia. This apparent difference might be explained by the fact that the present study actually missed an initial 'slow perfusion' phase preceding the hyperaemic phase that was assessed at 30 min after reperfusion. Interestingly, skin blood flow returned to near-baseline values at 1 h of reperfusion following 2 h of hind limb ischaemia, which is in line with Hardy's results in the muscle. From that moment, there was an ongoing decrease in skin venular blood flow in the 2-h ischaemia group up to 4 h after reperfusion. Hardy *et al.* described such a decrease in muscle perfusion in a 6-h ischaemia group only. It may be argued that the skin is more susceptible to ischaemic injury than muscle. The no-reflow phenomenon that was reported by Menger *et al.*[33] in striated muscle was not observed. This may be explained by the relatively short periods of ischaemia in the present study. Other reports suggest that in the skin only ischaemic intervals of 6 h or more induce a reperfusion that is characterized by capillary no-reflow[13].

In this model of acute limb I/R, the effects on the microcirculation can be assessed non-invasively in the skin only. Since the extent of hind limb muscle injury is a critical determinant of morbidity and mortality in patients with limb I/R injury, the muscular microcirculation has been an important focus of other pathophysiological studies[10,12,13]. Although the exact time course of changes in skin and skeletal muscle might be different, the same pathological mechanisms have been reported to underlie changes in skin and muscle microcirculation[13]. In the present study a relation was found between the levels of leucocyte adherence in the skin and infiltration in the tibial muscle. This suggests that in both tissues similar early inflammatory reactions are induced by the I/R protocol which may contribute to local tissue injury.

As future research on the revascularization syndrome will be focused more on the underlying pathophysiological mechanisms and its pharmacological treatment, the present model may be used to perform mechanistic studies aimed at intervening in leucocyte–endothelial interactions. Leucocyte–endothelial interactions play an important role in I/R injury[5], and are mediated by several classes of adhesion molecule, all expressed in a unique time-dependent pattern[5,22,25]. The use of specific adhesion molecule blockers in this model will enable the study of their efficacy over time in case of acute limb I/R. Since this model allows multiple serial observations and measurements, it is also well suited for mechanistic investigation of the phenomenon of ischaemic preconditioning[34].

Acknowledgements

The authors acknowledge the assistance of M. J. A. P. Daemen, Department of Pathology, University Hospital Maastricht, and the technical assistance of S. van Velzen, Department of Physiology, Maastricht University. They are also grateful to three student research assistants who each helped with aspects of the study: M. A. Selis, B. P. L. Witteman and S. G. M. Rutten.

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Recombinant soluble P-selectin glycoprotein ligand 1 moderates local and remote injuries following experimental lower-torso ischaemia

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Background: A central role for the polymorphonuclear leucocyte (PMN) in skeletal muscle ischaemia–reperfusion has been demonstrated by the observation that PMN depletion reduced local and remote pulmonary vascular permeability. This study investigated the role of recombinant soluble P-selectin glycoprotein ligand–immunoglobulin fusion protein (rPSGL-Ig), a P- and E-selectin antagonist, in moderating injury.

Methods: Mice underwent 2 h of hindlimb ischaemia and 3 h of reperfusion. Muscle and lung vascular permeability index (PI) was assessed by extravasation of ^{125}I-radiolabelled albumin. Lung myeloperoxidase (MPO) activity was also measured.

Results: In mice treated with rPSGL-Ig 1 mg/kg before reperfusion (*n* = 12) muscle PI was reduced by 40 per cent, whereas it was moderated by 20 per cent in animals treated 30 min after reperfusion (*n* = 15). Lung PI in mice treated with rPSGL-Ig before (*n* = 12) and 30 min after (*n* = 15) reperfusion was reduced by over 99 and 98 per cent respectively. Lung MPO activity in mice treated with rPSGL-Ig before (*n* = 10) and 30 min after (*n* = 12) reperfusion was reduced by 68 and 58 per cent respectively. Treatment with rPSGL-Ig 1 h after reperfusion, or with m20ek.Fc 1 mg/kg (*n* = 9; negative control for rPSGL-Ig which is inactive for selectin binding) before reperfusion failed significantly to moderate local or remote organ injury.

Conclusion: Selectin blockade moderated local skeletal muscle and remote lung injury following hindlimb ischaemia–reperfusion. Significantly, delayed antiselectin therapy also decreased injury.

Presented to the Surgical Research Society in Cork, Ireland, October 2000, and published in abstract form as *Br J Surg* 2001; 88: 746–747

Paper accepted 11 February 2001

British Journal of Surgery 2001, 88, 825–830

Introduction

After lower-torso ischaemia, reperfusion can lead to multi-organ injury[1]. Local events include endothelial damage and permeability oedema[2]. Remote organ injury is characterized by increased pulmonary vascular permeability and neutrophil sequestration[3].

Experimental models of hindlimb ischaemia–reperfusion have identified the polymorphonuclear leucocyte (PMN) as playing a central role in subsequent organ damage[1,4]. PMN immunodepletion before the ischaemia moderates both local and remote organ injury[2,3]. Neutrophil–endothelial cell interaction via adhesion molecules is a prerequisite for microvascular injury. The selectin family of adhesion molecules is responsible for the initial tethering of PMNs to the microvessels[5]. Rolling neutrophils become activated and firmly attached to the endothelium via β_2-integrin interaction with intercellular adhesion molecules (ICAMs) 1 and 2[6]. Their activation leads to increased microvascular permeability by the release of free radicals and proteolytic enzymes.

Experimental antiselectin therapy using sialyl-Lewis^x (sLe^x) or P-selectin antibody moderates local skeletal muscle reperfusion injury in the rat[7]. Also, anti-integrin therapy in the form of a Mac-1 (CD11b) antibody reduces remote lung injury following intestinal and skeletal muscle ischaemia–reperfusion in the rat[8].

This study investigated the role of recombinant soluble P-selectin glycoprotein ligand–immunoglobulin fusion protein (rPSGL-Ig), a P- and E-selectin antagonist, in reducing local skeletal muscle and remote pulmonary injury following hindlimb ischaemia–reperfusion. In addition, the role of delayed selectin blockade in moderating injury was investigated.

Materials and methods

Recombinant proteins

rPSGL-Ig (Genetics Institute, Cambridge, Massachusetts, USA) was derived from pED.47.Fc, a recombinant soluble form of PSGL-1 fused to human IgG_1[9]. Polymerase chain reaction (PCR) was performed on the Fc portion of this plasmid using 5′ primer TAAATAGCGGCCGCACACATGCCCACCGTGCCCAGCACCTGAAGCCCTGGGGGCACCGTCAGTCTTCCTC and 3′ primer GCATGTTGCACCGAGGCCCCAGAATCA. The PCR product was digested with the restriction enzymes *Not*I and *Kpn*I, and ligated to the large fragment of pED.47.Fc restricted with the same digest. The resulting vector, pED.47mutFc, was confirmed by DNA sequencing and then stably transfected and amplified in a dihydrofolate reductase-negative Chinese hamster ovary cell line that had previously been stably transfected with vector pMT4neo expressing both the complementary DNA (cDNA) encoding an α(1,3/1,4)fucosyltransferase and a cDNA encoding core 2β-1,6-*N*-acetylglucosaminyltransferase[9]. Analysis of several resulting clonal cell lines revealed a cell line with readily detectable core 2, fucosyltransferase activities and sLe^x-modified glycans on 47mutFc: rPSGL-Ig. Endothelial selectin binding activity was confirmed by utilizing *in vitro* binding assays as described previously[9].

m20ek.Fc (Genetics Institute) recombinant protein has the sequence QVVGDDDFEDPDYTYNTDPPDDDDKAPRA, consisting of the mature amino-terminal 20 amino acids of murine PSGL-1, followed by an enterokinase cleavage site, then fused to an Ala234/Ala237-mutated form of human IgG_1 Fc[10]. The murine PSGL segment lacks critical *O*-linked glycans and is therefore inactive for selectin binding, as confirmed by *in vitro* binding assays described previously[9]. m20ek.Fc was used as the negative control for rPSGL-Ig.

Animals

Male C57BL/6 mice aged 8–12 weeks and weighing 25–30 g, purchased from Taconic Farms (Germantown, New York, USA) were used for all experiments. The animals were maintained in accordance with the guidelines of the Committee on Animals of Harvard Medical School and those prepared by the Committee on the Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources National Research Council.

Hindlimb model of ischaemia–reperfusion injury

Mice were anaesthetized with intraperitoneal sodium pentobarbital 60 mg/kg and underwent 2 h of hindlimb ischaemia, followed by 3 h of reperfusion. After 2 min of hindlimb elevation to minimize retained blood, bilateral rubber bands (latex O rings) were applied above the greater trochanter, using a McGivney Hemorrhoidal Ligator (Miltex Instrument Company, Lake Success, New York, USA). Sham mice did not undergo ischaemia. Five minutes before rubber band release, animals received 1 μCi ^{125}I-radiolabelled albumin (ICN, Irving, California, USA) in 0·3 ml of 0·9 per cent saline via tail vein injection. Hydration was maintained by intravenous infusion of 0·1 ml of 0·9 per cent saline during each hour of reperfusion. Mice were maintained in a supine position and kept anaesthetized by intermittent intraperitoneal sodium pentobarbital injections. They were covered throughout the experiment to maintain body temperature. The experimental mortality rate was less than 10 per cent in mice undergoing ischaemia–reperfusion and zero in animals undergoing sham injury. The animals were killed with an overdose of intraperitoneal sodium pentobarbital (90 mg/kg), blood was aspirated from the right ventricle through a midline sternotomy and its γ radioactivity was counted (Packard, Downes Grove, Illinois, USA).

Muscle permeability

Muscle was harvested from both hindlimbs, its radioactivity measured and it was then dried to a constant weight in a gravity convection oven (Precision Scientific Group, Chicago, Illinois, USA) at 90°C for 72 h. Extravasation of ^{125}I-labelled albumin was used to assess the hindlimb vascular permeability index (PI), which was determined by the ratio of radioactivity per gram of dry muscle to radioactivity per gram of blood.

Pulmonary permeability

Tracheostomies were performed using a 16-G catheter (Angiocath; Becton-Dickinson, Sandy, Utah, USA) and the lungs were instilled with 0·5 ml of 0·9 per cent saline using a 1-ml syringe. After 1 min, the bronchoalveolar (BAL) fluid was aspirated. This process was performed three times over 3 min using a total of 1·5 ml saline. A mean(s.e.m.) total of 0·9(0·1) ml of BAL fluid was retrieved. Lung PI was reported as the ratio of radioactivity per gram of BAL fluid retrieved to radioactivity per gram of blood.

Lung myeloperoxidase assay

Myeloperoxidase (MPO) activity was determined according to the method described by Schierwagen *et al.*[11]. In animals not receiving ^{125}I-radiolabelled albumin, lung specimens were collected, cleaned and frozen at – 70°C for later MPO analysis, to quantify neutrophil sequestration. MPO is a haem-containing enzyme stored within the azurophilic granules of neutrophils, constituting 5 per cent of their dry weight. At the time of assay, samples were thawed at room temperature, rinsed with phosphate-buffered saline, blotted dry and weighed. Tissue buffer (potassium phosphate buffer 0·05 mol/l containing 0·5 per cent hexadecyltrimethyl-ammonium bromide (Sigma, St Louis, Missouri, USA), pH 6·0) was added and the lung tissue homogenized. The samples were sonicated twice for 10 s and then centrifuged at 20 000*g* for 15 min at 4°C. The supernatant was incubated in a water bath at 50°C for 2 h and then diluted for assay. A standard curve was constructed by serial dilution of a human MPO standard (Biogenesis, Poole, UK) in tissue buffer. The assay was conducted in a 96-well microtitre plate containing 25 µl tissue sample (or MPO standard), 25 µl tetramethylbenzidine dihydrochloride (Aldrich, Milwaukee, Wisconsin, USA) and 200 µl potassium phosphate assay buffer 0·08 mol/l containing hydrogen peroxide 0·3 mmol/l, pH 5·4. The plate was shaken for 30 s and incubated at 37°C for 5 min. The reaction was stopped by adding 25 µl bovine catalase (Sigma) from a stock solution (13·6 mg bovine catalase in 100 ml deionized water). The plate was again shaken and read at 650 nm.

Treatment with recombinant proteins

Mice were treated with rPSGL-Ig, administered intravenously 5 min before reperfusion, as endothelial selectin activation occurs in response to inflammatory mediators produced during reperfusion[9,12,13]. Each animal received rPSGL-Ig 1 mg/kg, a dose previously determined to inhibit neutrophil–selectin interaction effectively[2,3] and lasting for more than 4 h[9]. Another group of mice received m20ek.Fc 1 mg/kg intravenously 5 min before reperfusion. Additional groups of animals were treated with an intravenous bolus of rPSGL-Ig, 30 min or 1 h after reperfusion, but not before.

Statistical analysis

Results were presented as mean(s.e.m.). Significance between groups was first tested by one-way analysis of variance and, if significance was found, Student's *t* test with the Bonferroni correction for multiple comparisons was applied. Percentage reduction in PI and MPO activity was calculated after subtraction of the background value determined in sham animals.

Results

Local muscle permeability (*Fig. 1*)

Reperfusion of the ischaemic skeletal muscle resulted in vascular injury, manifested by the extravasation of radio-labelled albumin. The PI in mice ($n = 17$) after 3 h of reperfusion was 2·51(0·16), significantly higher than the PI of 0·17(0·01) in sham-operated animals ($n = 10$) ($P < 0{\cdot}05$). Treatment with rPSGL-Ig 5 min before reperfusion ($n = 12$) reduced permeability by 40 per cent ($P < 0{\cdot}05$), indicating the importance of selectin-mediated neutrophil adhesion and activation. The PI was not significantly

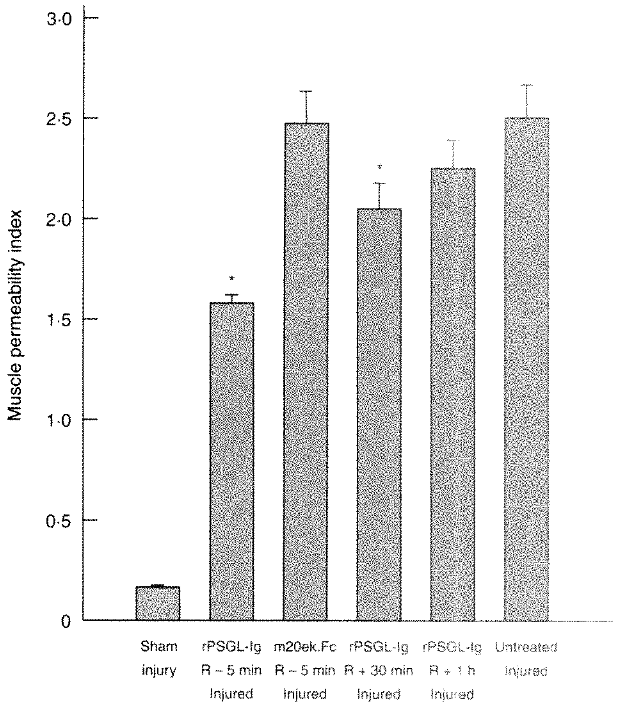

Fig. 1 Moderation of skeletal muscle reperfusion injury by endothelial selectin blockade. Sham mice did not undergo hindlimb ischaemia. Treatment with recombinant soluble P-selectin glycoprotein ligand–immunoglobulin fusion protein (rPSGL-Ig) 5 min before reperfusion (R – 5 min) reduced the permeability index (PI) by 40 per cent. Treatment with m20ek.Fc, a negative control for rPSGL-Ig which is inactive for selectin binding, failed to moderate injury. Treatment with rPSGL-Ig 30 min after reperfusion (R + 30 min) reduced the PI by 20 per cent. No significant reduction in permeability was noted in mice treated with rPSGL-Ig 1 h after reperfusion (R + 1 h). Values are mean(s.e.m.). *$P < 0{\cdot}05$ *versus* untreated injured mice (Student's *t* test)

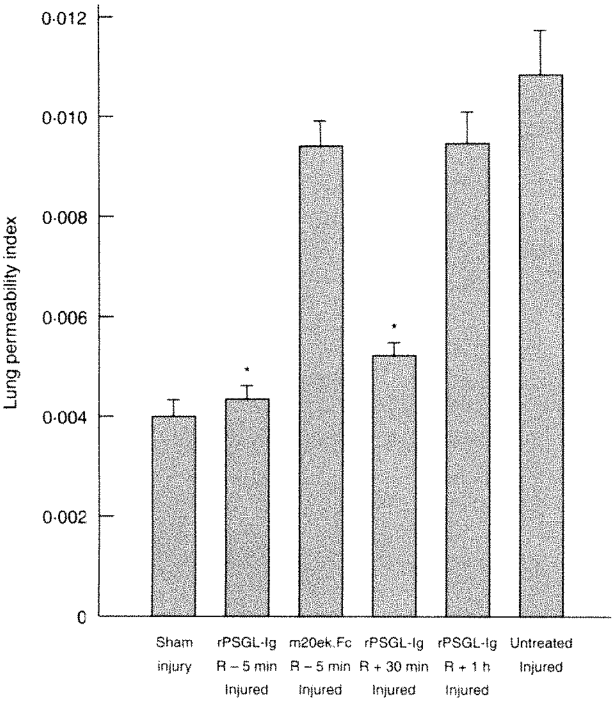

Fig. 2 Moderation of remote lung injury by endothelial selectin blockade. Sham mice did not undergo hindlimb ischaemia. Treatment with recombinant soluble P-selectin glycoprotein ligand–immunoglobulin fusion protein (rPSGL-Ig) 5 min before reperfusion (R – 5 min) reduced the permeability index (PI) by over 99 per cent. Treatment with m20ek.Fc, a negative control for rPSGL-Ig which is inactive for selectin binding, failed to moderate injury. Treatment with rPSGL-Ig 30 min after reperfusion (R + 30 min) reduced the PI by 98 per cent. No significant reduction in permeability was noted in mice treated with rPSGL-Ig 1 h after reperfusion (R + 1 h). Values are mean(s.e.m.). *$P < 0{\cdot}05$ *versus* untreated injured mice (Student's *t* test)

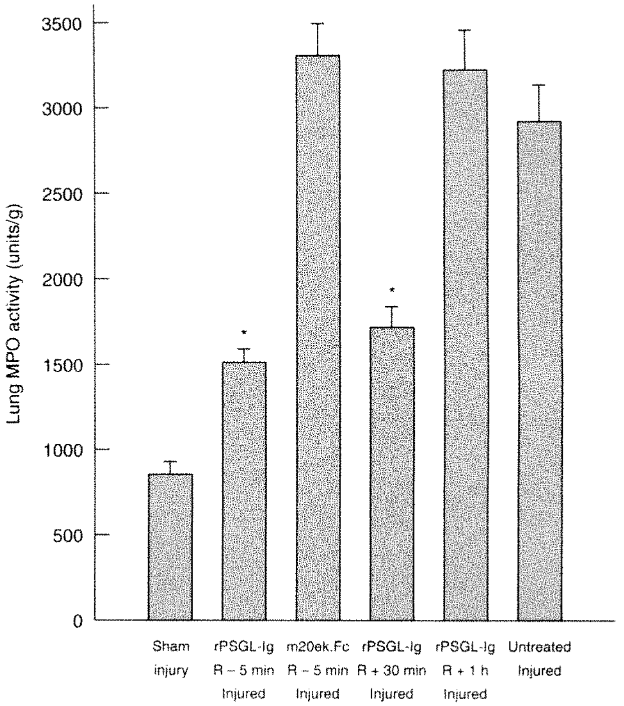

Fig. 3 Moderation of remote lung neutrophil sequestration by endothelial selectin blockade. Sham mice did not undergo hindlimb ischaemia. Treatment with recombinant soluble P-selectin glycoprotein ligand–immunoglobulin fusion protein (rPSGL-Ig) 5 min before reperfusion (R – 5 min) reduced lung myeloperoxidase (MPO) activity by 68 per cent. Treatment with m20ek.Fc, a negative control for rPSGL-Ig which is inactive for selectin binding, failed to moderate MPO activity. Treatment with rPSGL-Ig 30 min after reperfusion (R + 30 min) reduced MPO activity by 58 per cent. No reduction in MPO activity was noted in mice treated with rPSGL-Ig 1 h after reperfusion (R + 1 h). Values are mean(s.e.m.). *$P < 0{\cdot}05$ *versus* untreated injured mice (Student's *t* test)

moderated in animals treated with m20ek.Fc ($n = 9$), which is inactive for selectin binding. The PI in mice treated with rPSGL-Ig 30 min after reperfusion ($n = 15$) was reduced by 20 per cent ($P < 0{\cdot}05$), whereas in animals treated with rPSGL-Ig 1 h after reperfusion ($n = 11$) it was not significantly moderated compared with that in the untreated group.

Pulmonary permeability (*Fig. 2*)

The PI in mice following sham ischaemia was 0·0040(0·0003). Ischaemia–reperfusion led to a marked rise in PI to 0·0108(0·0018) ($P < 0{\cdot}05$). Antiselectin therapy with rPSGL-Ig 5 min before reperfusion reduced permeability by over 96 per cent but the PI was not significantly moderated in animals treated with m20ek.Fc. The PI in mice treated with rPSGL-Ig 30 min after reperfusion was reduced by 82 per cent ($P < 0{\cdot}05$), whereas in animals treated with rPSGL-Ig 1 h after reperfusion the PI was not significantly different from that in the untreated group.

Lung myeloperoxidase activity (*Fig. 3*)

MPO activity within the lungs increased from 849(79) units/g in sham animals ($n = 6$) to 2919(212) units/g in mice with reperfusion injury ($n = 15$) ($P < 0{\cdot}05$). Treatment with rPSGL-Ig 5 min before reperfusion ($n = 10$) reduced MPO activity by 68 per cent ($P < 0{\cdot}05$). MPO activity was not moderated in animals treated with m20ek.Fc ($n = 9$). In mice treated with rPSGL-Ig 30 min after reperfusion ($n = 12$) MPO activity was reduced by 58 per cent compared with that in the untreated group ($P < 0{\cdot}05$). MPO activity in animals treated with rPSGL-Ig 1 h after reperfusion (n = 9) was not altered.

Discussion

A central role for the neutrophil in mediating the local events in reperfusion injury after tissue ischaemia has been documented in a number of organs including skeletal muscle[1,14]. Neutrophil diapedesis and sequestration within reperfused tissues is facilitated by adhesion to the microvascular endothelium[1]. The adhesion sequence of events starts with leucocyte rolling and tethering on the endothelial cell, which is mediated by the selectin family of adhesion molecules[5]. P-selectin stored in Weibel–Palade bodies is rapidly translocated on the endothelial cell surface following stimulation by various chemoactivators[15]. E-selectin is upregulated later on the endothelium in response to the cytokines interleukin 1 and tumour necrosis factor (TNF) α[16]. L-selectin is expressed constitutively on the leucocytes and is shed rapidly following their activation[17]. Each selectin binds to a glycoprotein counter-receptor expressing sLe^x-related oligosaccharides such as PSGL-1[18]. After this initial selectin interaction, leucocyte β_2-integrins upregulated by agents such as C5a, TNF-α and platelet-activating factor form firm adhesions with endothelial cell ICAM-1 and -2[19]. Local chemoattractants such as the complement fragment C5a and the arachidonic acid metabolites, leukotriene B_4 and thromboxane A_2, produced in high concentrations at the site of endothelial injury, are potent stimuli for PMN generation of hydrogen peroxide and elastase, and can facilitate PMN diapedesis[20].

The experimental use of antiselectin immunotherapy has been shown to moderate skeletal muscle reperfusion injury[12]. Weiser *et al.*[7] reported in a rat model of hindlimb ischaemia–reperfusion that antiselectin therapy in the form of a P-selectin antibody reduced permeability by 26 per cent, although this was less than the 36 per cent decrease noted with infusion of the oligosaccharide sLe^x, a more general selectin antagonist, at a dose of 10 mg/kg. The present data confirm that broad selectin antagonism produced by a soluble form of the selectin counter-receptor PSGL-1 reduces local muscle permeability by 40 per cent, which suggests that there is overlapping function of the selectin adhesion molecules. Furthermore, in this model rPSGL-Ig abrogated PMN-mediated injury at one-tenth of the dose of sLe^x, suggesting a more potent selectin antagonism.

Following ischaemia, local tissue reperfusion generates a number of inflammatory mediators that activate circulating neutrophils and remote endothelium. Lung leucosequestration occurs progressively over several hours, an event associated with permeability oedema[3]. In this study evidence was provided that neutrophil-mediated lung injury which occurs as a consequence of lower-torso ischaemia–reperfusion is facilitated by selectin–PMN interaction. Seekamp *et al.*[12], using antiselectin antibodies in a rat model of 4 h of hindlimb ischaemia followed by 4 h of reperfusion, reported that lung injury was L- and E-selectin dependent. When ischaemia and reperfusion times were reduced to 1 and 1·5 h respectively, lung injury was also P-selectin dependent. Injury was blocked by infusion of the general selectin antagonist sLe^x. These data appear to be in agreement with the present findings, where lung permeability following 2 h of hindlimb ischaemia and 3 h of reperfusion was reduced to the sham value with rPSGL-Ig, which possesses both P- and E-selectin-binding properties[9].

In this study, PMN sequestration was reduced by 68 per cent in the lungs of animals treated with rPSGL-Ig. Because it is a specific ligand for selectins, rPSGL-Ig presumably acted by inhibiting the binding between endothelial cell selectins and neutrophils with the PSGL-1 counter-receptor. Takada *et al.*[13], in a rat model of kidney ischaemia–reperfusion, demonstrated that rPSGL-Ig, in addition to blocking local PMN infiltration by 50 per cent, reduced the induction of E-selectin messenger RNA (mRNA) in that organ. The authors concluded that this event was predominantly mediated by rPSGL-Ig blocking P-selectin, which may diminish the local production of proinflammatory cytokines that induce E-selectin expression. Without initial tethering, later integrin interaction with ICAM leading to PMN activation would be unlikely to take place. Scalia *et al.*[21], in a rat model of Noble–Collip drum traumatic shock, found that infusion of rPSGL-Ig inhibited *de novo* synthesis of leucocyte PSGL-1 as indicated by low blood levels of PMN mRNA. The authors concluded that the mode of action of rPSGL-Ig may be extended not only to inhibition of leucocyte–endothelial interaction but also to attenuation of leucocyte–leucocyte and leucocyte–platelet interactions. These mechanisms are thought to be involved in PMN-mediated organ injury during ischaemia–reperfusion.

Finally, the likely role of delayed endothelial selectin blockade was studied, as this may have significant clinical implications, since treatment often takes place during the reperfusion phase of injury. Significantly, the present data suggest that there may be a therapeutic window of 30 min after reperfusion, during which delayed administration of rPSGL-Ig can still lead to effective antagonism of PMN–selectin adhesion, leading to a reduction in local and remote permeability oedema as well as neutrophil accumulation within the lungs. This protective effect was lost after 1 h, indicating that PMN activation and adhesion mechanisms were no longer selectin dependent.

Acknowledgements

The authors thank Mr Gray Shaw of the Genetics Institute, Cambridge, Massachusetts, for the generous donation of rPSGL-Ig and m20ek.Fc used in the experiments. This work was supported in part by the National Institutes of Health grants GM-07560, GM-52585, GM-35141-09 and GM-2489-18, the Brigham Surgical Group and the Trauma Research Foundation.

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Original article

Use of minilaparotomy in the treatment of colonic cancer

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Background: The feasibility and safety of a minilaparotomy approach for curative resection of colonic cancer have not been fully elucidated. The purpose of this study was to compare outcomes utilizing this alternative technique with those of conventional laparotomy.

Methods: Eighty-four patients scheduled to undergo resection for colonic cancer via minilaparotomy between 1997 and 1999 were studied prospectively. The minilaparotomy involved complete resection performed through a skin incision less than 7 cm in length. Sixty-nine patients who underwent a similar resection via a conventional laparotomy between 1994 and 1996 served as the control group.

Results: The minilaparotomy approach was successful in 72 of 84 patients. Colectomy type, operating time and histopathological features of tumours were similar between cases and controls, whereas operative blood loss in the control group was significantly greater ($P = 0{\cdot}002$). Postoperative times to standing, walking, passage of flatus and urinary catheter removal were significantly shorter in the minilaparotomy group ($P = 0{\cdot}007$, $P = 0{\cdot}003$, $P = 0{\cdot}03$ and $P = 0{\cdot}006$ respectively), and analgesic requirements were significantly lower ($P = 0{\cdot}001$). At a median follow-up of 24·8 months there have been no tumour recurrences at the minilaparotomy incision sites.

Conclusion: A minilaparotomy approach to the curative resection of colonic cancer is an attractive alternative to conventional laparotomy in selected patients.

Paper accepted 31 December 2000

British Journal of Surgery 2001, **88**, 831–836

Introduction

Laparoscopically assisted colectomy may result in a more rapid return of bowel function, attainment of preoperative status and earlier hospital discharge compared to traditional laparotomy[1–5]. Reasons proposed for the more rapid recovery after laparoscopically assisted colorectal surgery include a reduction in operation-induced stress, decreased postoperative pain and smaller abdominal incisions[6]. At completion of most laparoscopic colectomies, a small incision is made for extracorporeal anastomosis and removal of the specimen after laparoscopic mobilization of the bowel[7]. Fleshman *et al.*[6] evaluated the minilaparotomy approach and showed that laparoscopically assisted surgery for colorectal diseases did not confer added benefit. They concluded that rapid return of bowel function and earlier patient discharge were dependent on the use of small incisions, whether by minilaparotomy or laparoscopy[6].

The aims of this prospective study were to assess the feasibility and safety of using a minilaparotomy technique (length of incision less than 7 cm) in curative resection of patients with colonic cancer, and to compare various outcomes with those of conventional resection through a laparotomy incision.

Patients and methods

Definition of minilaparotomy

The minilaparotomy approach for the treatment of colonic cancer was defined as complete resection performed through a skin incision less than 7 cm in length.

Patient selection

Eighty-four patients (38 women, 46 men; median age 68 (range 39–88) years) were enrolled in this prospective study and scheduled to undergo complete resection for colonic cancer using the minilaparotomy approach between January 1997 and December 1999. Excluded from the study were patients who did not consent to the procedure, those with a tumour larger than 6 cm in size or infiltrating adjacent organs, patients who had intestinal obstruction or perforation, those with synchronous cancers or familial adenomatous polyposis, and patients who had metastases to the liver, para-aortic lymph nodes or other distant organs.

The control group comprised 69 patients with colonic cancer matching the preoperative exclusion criteria mentioned above who had undergone colonic resection by conventional laparotomy (using a median incision) between January 1994 and December 1996.

Preoperative management

A uniform method of preoperative care, including diet counselling and directions regarding pulmonary function, was used in all patients. Some 2–3 litres of polyethylene glycol electrolyte solution given 1 day before operation served as bowel preparation. Urinary catheters and nasogastric tubes were used routinely. Epidural catheters were placed before induction of anaesthesia for both intraoperative and postoperative use.

Operative technique

The patient was placed in the supine or lithotomy position. All steps of the minilaparotomy approach were performed using conventional surgical techniques and instruments via a small abdominal incision. A right transrectus, left transrectus or lower median skin incision less than 7 cm in length was used for cancers of the right colon, left colon or distal sigmoid colon respectively. The choice of incision was determined in a manner intended to facilitate the most straightforward resection.

Several large gauze swabs were inserted into the abdominal cavity to retract the small bowel and omentum from the operative field and an OMNI-TRACT® retractor system (Omni-Tract Surgical, Minneapolis, Minnesota, USA) was used. With this approach, division of the central vessels at their origin and removal of the draining lymph nodes was facilitated. By moving the minilaparotomy wound laterally and caudad or cephalad, cautious mobilization of the relevant segment of bowel loop was performed. The colon and its mesentery were carefully externalized through the minilaparotomy wound, allowing division of the associated mesentery and transection of the bowel with adequate proximal and distal margins to be performed extracorporeally. Lastly, bowel continuity was restored by means of hand-sewn or stapled anastomosis.

Postoperative care

Similar criteria for postoperative management were used in both groups. Diet was resumed after operation as soon as bowel function returned clinically. Analgesia (pentazocine) was administered intramuscularly as required. When fully ambulatory, patients were discharged. Data for patients having a minilaparotomy were collected prospectively, whereas data for those having a conventional approach were retrieved retrospectively. American Joint Committee on Cancer classification and stage grouping were used to grade the tumours[8]. Median (range) length of follow-up in the minilaparotomy and conventional groups was 24·8 (7·3–46·3) and 53·7 (10·5–82·5) months respectively. No patient was lost to follow-up.

Statistical analysis

Continuous data were expressed as median (interquartile range (i.q.r.) and analysed with the Mann–Whitney *U* test. Categorical data were analysed by χ^2 test or Fisher's exact test. Disease-free and disease-specific survival rates were calculated according to the Kaplan–Meier method[9], and differences between survival curves were tested for significance with the log rank test[10]. All tests were two tailed and $P < 0.05$ was considered significant.

Results

Feasibility of the minilaparotomy approach

Of the 84 patients who were to undergo complete resection for colonic cancer using the minilaparotomy approach, success was achieved in 72 (86 per cent) and failure occurred in 12 (14 per cent). The reasons for failure were: inability to divide the lienocolic and phrenocolic ligaments at the splenic flexure (five patients), tumour adhesion or invasion into adjacent organs (five) and the presence of intra-abdominal adhesions due to previous laparotomy (one). In one patient the tumour was too large to allow removal through the minilaparotomy incision.

Patient population

The surgical outcomes of successful minilaparotomy in 72 patients and the conventional laparotomy approach in 69 patients were compared. Patient characteristics were similar between the two groups (*Table 1*).

Operative procedures

The length of the laparotomy incision in the minilaparotomy group was significantly shorter than that in patients having the conventional approach ($P < 0.001$). Operating times were similar, although operative blood loss was greater in patients having the conventional operation than in the minilaparotomy group ($P = 0.002$). The type of

Table 1 Characteristics of patients

	Minilaparotomy ($n = 72$)	Conventional ($n = 69$)	P
Age (years)*	68 (60–74)	68 (60–74)	0·84‡
Sex†			0·50§
Female	33 (46)	27 (39)	
Male	39 (54)	42 (61)	
Body-weight (kg)*	54·5 (46·7–61·5)	53·5 (48·0–61·0)	0·82‡
Height (cm)*	157·3 (149·9–164·7)	157·5 (151·0–163·0)	0·93‡
BMI (kg/m^2)*	22·1 (20·1–24·3)	21·8 (20·1–23·6)	0·59‡
Previous laparotomy†	25 (35)	26 (38)	0·73§
Tumour location†			0·31§
Right colon	27 (38)	32 (46)	
Left colon	45 (62)	37 (54)	

*Values are median (interquartile range); †values in parentheses are percentages; ‡Mann–Whitney *U* test; §χ^2 test

Table 2 Operative procedures

	Minilaparotomy ($n = 72$)	Conventional ($n = 69$)	P
Length of laparotomy wound (cm)*	7·0 (4·0–7·0)	20·0 (18·0–20·0)	< 0·001‡
Operating time (min)*	170·0 (150·0–203·0)	185·0 (155·0–215·0)	0·14‡
Operative blood loss (ml)*	43·0 (22·5–80·0)	63·0 (35·0–130·0)	0·002‡
Operation†			0·95§
Ileocaecal resection	10 (14)	15 (22)	
Right hemicolectomy	11 (15)	13 (19)	
Transverse colectomy	6 (8)	3 (4)	
Left partial colectomy	3 (4)	5 (7)	
Sigmoid colectomy	42 (58)	33 (48)	
Anastomosis†			0·35§
Hand-sewn	59 (82)	61 (88)	
Stapled	13 (18)	8 (12)	

*Values are median (interquartile range); †values in parentheses are percentages; ‡Mann–Whitney *U* test; §χ^2 test

colectomy and anastomosis performed did not differ between groups (*Table 2*).

Histopathological features of tumours

Histopathological parameters, such as maximum tumour diameter, number of lymph nodes removed, assessment of proximal and distal margins, histological type and stage, were similar for the two groups. The minilaparotomy and conventional groups included 32 and 31 patients with stage I, 24 and 21 patients with stage II, and 16 and 17 patients with stage III disease respectively.

Postoperative events

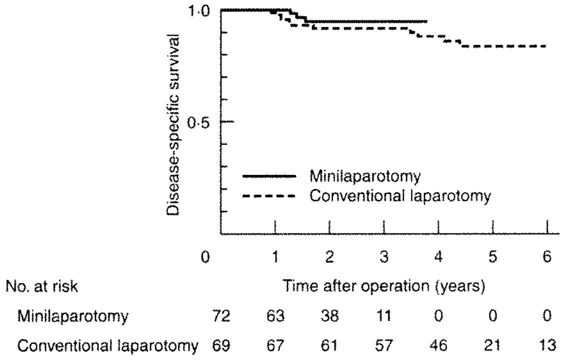
Postoperative intervals until first standing, walking, passage of flatus and urinary catheter removal following the minilaparotomy approach were significantly shorter than after conventional surgery (*Table 3*). However, time to tolerance of liquid and solid diet did not differ between the two groups.

All patients in both groups received pain relief by means of continuous epidural anaesthesia (mepivacaine hydrochloride plus buprenorphine hydrochloride) and intramuscular injections of pentazocine as required. The median (i.q.r.) duration of indwelling epidural catheter use was 4 (3·0–4·0) days in both groups. The median dosage of mepivacaine hydrochloride and buprenorphine hydrochloride administered through the epidural catheter was not significantly different between groups. Patients in the conventional group required more analgesia than those in the minilaparotomy group ($P = 0·001$). In the minilaparotomy group, analgesic requirements (pentazocine) in patients with transrectus incisions and median incisions did not differ significantly. Postoperative length of hospital stay did not differ between the two groups.

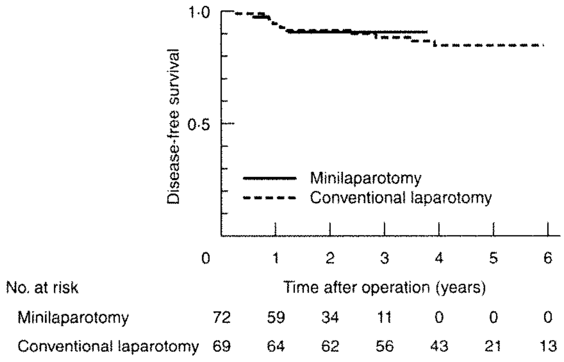
Table 3 Postoperative course

	Minilaparotomy (*n* = 72)	Conventional (*n* = 69)	*P**
Time to standing (days)	2 (1–2)	2 (1–3)	0·007
Time to walking (days)	2 (1–2)	3 (2–3)	0·003
Time with urinary catheter (days)	2 (1–3)	2 (2–4)	0·006
Time to passage of flatus (days)	2 (2–3)	3 (2–3)	0·034
Time to liquid food (days)	4 (3–5)	4 (4–5)	0·087
Time to solid food (days)	6 (5–7)	6 (5–7)	0·07
Analgesic (pentazocine) usage (mg)	0 (0–0)	15 (0–30)	0·001
Postoperative hospital stay (days)	14 (12–17)	13 (11–17)	0·51

Values are median (interquartile range). *Mann–Whitney *U* test



a Disease-specific



b Disease-free

Fig. 1 Comparison of **a** disease-specific survival and **b** disease-free survival of patients in the minilaparotomy and conventional approach groups. The disease-specific or disease-free survival time of patients did not differ between the two groups ($P = 0{\cdot}51$ and $P = 0{\cdot}85$ respectively; log rank test)

Postoperative complications

There was no operative mortality in either group. Five patients (7 per cent) in the minilaparotomy group developed complications: intestinal obstruction (three patients), wound infection (one) and subcutaneous haematoma at the laparotomy wound (one). Seven patients (10 per cent) in the conventional group developed complications: intestinal obstruction (three patients), minor anastomotic leakage (one) and wound infection (three). The frequency of postoperative complications between the two groups did not differ. One of three patients in the minilaparotomy group who developed intestinal obstruction underwent reoperation by means of a minilaparotomy 48 days after the initial operation.

Short-term surgical outcomes for cancer treatment

On completion of the study, 66 of 72 patients having the minilaparotomy approach were alive without tumour recurrence, and six (8 per cent) had developed tumour recurrence (metastasis to liver, lung and/or ovary), of whom three died. There have been no recurrences of tumour at the minilaparotomy incision site. In comparison, ten patients (14 per cent) in the conventional group had developed tumour recurrence, and five died from other causes. There have been no recurrences of tumour at the laparotomy site.

The disease-specific survival and disease-free survival rates of patients in the minilaparotomy and conventional approach groups are given in *Fig. 1*. The survival rates did not differ between the two groups.

Discussion

This prospective study demonstrates the feasibility and safety of a less invasive, minilaparotomy approach for curative resection of colonic cancer. This is a suitable technique in most patients, although not all patients are suitable candidates for resection via such a small incision. In this series the minilaparotomy approach was unsuccessful in 14 per cent of patients because of tumour size, tumour adhesion and/or invasion into adjacent organs, intra-abdominal adhesions due to previous laparotomy, or technical difficulty. In these patients the operation was completed by elongation of the incision or by means of laparoscopically assisted surgery without pneumoperitoneum[11] employing the original minilaparotomy incision. Thus, in some circumstances, a minilaparotomy may not be possible and a laparoscopically assisted technique may be a better choice. Fleshman *et al.*[6] claimed that patients for whom full visualization of the abdomen or mobilization of distant structures is required may be best suited to laparoscopy. The minilaparotomy, in which the incision can be moved horizontally or vertically for optimal visualization, may be best for local resection.

There is no consensus as to what comprises a minilaparotomy. Fürstenberg *et al.*[12] described a maximum incision length of 10 cm, whereas Fleshman *et al.*[6] included patients with 18-cm incisions as having undergone minilaparotomy. In the present series 7 cm was defined as the upper limit of incision length because this represented the minimum size that allowed insertion of the surgeon's hand into the peritoneal cavity. Thus, most colectomies can be performed via a smaller incision than surgeons generally believe.

The threshold of incision length that causes prolonged intestinal ileus has not been identified. Fleshman *et al.*[6] reported that return of bowel function was proportional to the length of the incision, as was degree of postoperative pain and time until discharge. Fürstenberg *et al.*[12] speculated that avoidance of small bowel manipulation reduces the time of postoperative paralysis. In the minilaparotomy approach, the small bowel was not exposed to the operating room environment.

The main reason for conversion from laparoscopic to open surgery is obesity[13], leading most surgeons to consider obesity a relative contraindication for laparoscopic colorectal resection[14]. Body mass index (BMI) has been used as an objective index to indicate morbid obesity, defined as a BMI[15] greater than 30[16,17]. Gatsoulis *et al.*[17] reported that 23 of 145 patients who underwent laparoscopic cholecystectomy were morbidly obese (BMI above 30), whereas in the present study only two of 72 patients met this definition. Also, in this study there was no difference in BMI between patients having minilaparotomy or the conventional approach. The frequency of morbid obesity in Japanese patients is less than that of patients in Western countries[18], thus a minilaparotomy approach may be a more suitable technique for Japanese patients with colonic cancer.

The main reported benefit of laparoscopic colonic surgery is reduction in the length of hospital stay[5]. In this study there was no difference in length of postoperative stay between minilaparotomy and conventional approaches. Japanese reports[19] also have shown no difference in the length of hospital stay when comparing patients with extensive lymph node dissection after laparoscopically assisted colectomy and colectomy by open laparotomy. Japanese patients, and the elderly in particular, demand hospital stays longer than the length recommended as necessary by their surgeons, and beyond that required for attainment of preoperative status. This may be attributed to a custom peculiar to Japan or to particularities regarding financial aspects of the Japanese healthcare system.

In conclusion, the minilaparotomy approach for the curative resection of colonic cancer is less invasive than the conventional technique and appears to represent an attractive alternative in selected patients with colonic cancer. However, there is a need for randomized studies to compare laparoscopic colonic surgery with minilaparotomy to define further the differences between these two modalities.

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Short note

Randomized study to examine the value of on-table inspection of the appendix mucosa

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Paper accepted 5 February 2001

Introduction

The standard incisions used for performing an appendicectomy do not permit a full laparotomy. The removal of a normal appendix, in the erroneous belief that it is inflamed, may result in the true pathology remaining undetected[1]. It is difficult, however, to accurately diagnose the presence of inflammation on simple inspection of the appendix, as approximately 10 per cent of apparently normal appendices are inflamed on subsequent histological examination[2]. It has been advocated traditionally that the appendix should be opened upon removal and its mucosa inspected for the presence of inflammation. Although this will theoretically distinguish true appendicitis from serosal inflammation induced by adjacent, extra-appendiceal pathology[3], the practice is not evidence based. Patients undergoing appendicectomy were therefore randomized with respect to whether the appendix was additionally opened at the time of removal. The surgeon's opinion on the state of the appendix was compared with the subsequent histological diagnosis. The results suggest that opening the appendix upon removal does not improve the accuracy of on-table diagnosis.

Patients and methods

Between August 1998 and February 1999, 120 consecutive patients underwent open appendicectomy for suspected acute appendicitis. Randomization was performed, using a random number table, as to whether inflammation was assessed, before fixation, simply from the external appearance of the appendix or whether the appendix was also opened. If opened, the presence of ulceration was considered indicative of inflammation. The appendix was then graded by the surgeon as being normal, mildly inflamed, moderately inflamed or severely inflamed (gangrenous or perforated). Histological examination was performed by one consultant pathologist. The minimum histological criterion required for the diagnosis of appendicitis was the presence of polymorphs within the mucosa or submucosa. The confidence interval for the difference between proportions was calculated according to the iterative method of Miettinen and Nurminen, using Arcus Quickstat software (Research Solutions, Cambridge, UK).

Results

The age and sex of the patients in the two groups were similar (data not shown). Ninety (75 per cent) of the 120 appendices removed were thought to be inflamed at the time of removal and this was confirmed histologically in 75 (83 per cent) (*Table 1*). Surprisingly, opening the appendix was associated with an increased likelihood of misdiagnosing a normal appendix as inflamed; this occurred nine times in the 'appendix opened' group as opposed to six times in the 'unopened' group (*Table 1*). This difference was not significant (95 per cent confidence interval for the difference in proportions −0·176 to 0·074, $P = 0·43$).

Discussion

Opening the appendix on table has been taught traditionally as being a necessary and integral part of an appendicectomy operation[3]. The results of this study suggest that it is unlikely to prevent occasions when appendicitis is wrongly diagnosed and the true pathology is missed. Opening the appendix cannot therefore be recommended, especially since it may compromise subsequent histological examination.

The greater number of false-positive surgical diagnoses in the 'appendix opened' group can be explained by assuming that mucosal inflammation alone, as occurs in early appendicitis, is distinguishable only upon microscopic, not macroscopic, examination. Trauma from opening the appendix may have been erroneously identified as inflammation.

Table 1 On-table diagnostic accuracy of opening the appendix compared with external inspection only

	Appendix opened ($n = 60$)	Appendix unopened ($n = 60$)
Surgically inflamed, histologically inflamed	38 (63)	37 (62)
Surgically normal, histologically normal	11 (18)	16 (27)
Surgically inflamed, histologically normal	9 (15)	6 (10)
Surgically normal, histologically inflamed	2 (3)	1 (2)

Values in parentheses are percentages

The surgeon labelled 29 appendices as severely inflamed, 48 as moderately inflamed and 13 as mildly inflamed. Histological examination confirmed the presence of inflammation in 29, 44 and only two respectively. This highlights the need for a more thorough laparotomy in patients whose appendix appears only mildly inflamed. They may benefit from additional laparoscopy, perhaps by using the wound as the site for entry of the port[4].

Acknowledgements
The authors thank Mr S. Singh for his review of the article, help and advice.

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Original article

Tumour location and the effects of preoperative radiotherapy in the treatment of rectal cancer

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Background: Preoperative radiotherapy improves local control and survival in rectal cancer, but may also increase postoperative morbidity and mortality rates. Establishing selection criteria for preoperative radiotherapy is crucial. The tumour level above the anus may be one such criterion. The effect of preoperative radiotherapy in relation to the distance between the tumour and the anus was therefore assessed.

Methods: In 457 patients operated for cure included in the Stockholm II Trial the local recurrence rate in irradiated and non-irradiated patients was analysed in relation to the tumour location (low, mid or upper rectum).

Results: Radiotherapy reduced the local recurrence rate from 30 to 20 per cent in low rectal cancer, from 25 to 11 per cent in mid rectal cancer and from 21 to 5 per cent for tumours in the upper rectum.

Conclusion: With conventional surgical techniques preoperative radiotherapy plays an important role in rectal cancer irrespective of the location of the tumour. To irradiate only patients with tumours in the lower rectum and to omit this treatment for patients with tumours in the mid and upper rectum cannot be recommended. Whether this statement is valid with standardized total mesorectal excision (TME) surgery is not known. Until this knowledge is available the current indications for preoperative radiotherapy should probably also be used with TME surgery.

Paper accepted 8 February 2001

British Journal of Surgery 2001, **88**, 839–843

Introduction

With surgery alone the local recurrence rate after potentially curative resection for rectal cancer has been high, ranging from 20 to 40 per cent[1–5]. To improve local control the effect of adjuvant radiotherapy in rectal cancer has been evaluated in several prospective randomized trials[6]. These trials have shown a significant reduction in the local recurrence rate with both preoperative and postoperative radiotherapy. However, preoperative radiotherapy seems to be more effective and the compliance is higher[7,8]. An overall survival benefit has also been shown with preoperative radiotherapy but not with postoperative radiotherapy, unless combined with chemotherapy[9]. Preoperative radiotherapy may, however, increase postoperative morbidity and mortality rates[10–12]. Therefore, the selection of patients for this treatment and the treatment technique is crucial. Patient selection criteria should be identified and the radiotherapy technique, dose and fractionation optimized.

As the risk of local recurrence increases with low rectal tumours[13–17] it may be argued that patients with tumours in the lower rectum should be irradiated while patients with tumours in the upper rectum may not need this treatment. Thus, the tumour level above the anus could be one selection criterion for preoperative radiotherapy.

To assess the effect of preoperative radiotherapy on the local recurrence rate in relation to the distance between the tumour and the anus, 457 patients operated for cure were reviewed. These patients had been included in the Stockholm II Trial, which prospectively evaluated preoperative radiotherapy *versus* surgery alone in the treatment of rectal cancer.

Patients and methods

The Stockholm II Trial was performed between 1987 and 1993. Details of the study have been published previously[18]. In summary, 557 patients with biopsy-proven adenocarcinoma of the rectum were randomized to preoperative irradiation followed by surgery or to surgery alone. Those allocated to radiotherapy received a total dose of 25 Gy (five fractions of 5 Gy) within a treatment time of 5 or 7 days (treatment interruption occurred for some patients over the weekend). Radiotherapy was given with a four-field technique and 6–21-MV linear accelerators were used. Exclusion criteria were a preoperative diagnosis of distant metastases, previous radiotherapy to the pelvis and age above 79 years.

Patient data, including tumour distance from the anal verge, the extent of surgery and findings of local, regional or distant spread, were reported prospectively by the responsible surgeon to the study secretariat. The height of the tumour (from the anal verge to the lower border of the tumour) was measured by rigid sigmoidoscopy. Details of tumour histopathology were reported by the responsible pathologist. Surgery was defined as curative if all macroscopic tumour was removed without signs of metastases and if the pathologist reported tumour-free margins of the specimen. During follow-up the surgeon reported findings of local recurrence, metastases, death and causes of death.

In all, 481 of 557 patients underwent a potentially curative procedure. In 24 of these patients the distance between the tumour and the anus was not reported conclusively so 457 patients were included in the present study. The low rectum was defined as 0–5 cm from the anorectal junction, the mid rectum as 6–10 cm and the upper rectum as more than 10 cm from the anorectal junction.

Statistical analysis

The relationship between tumour distance from the anus and clinical variables was analysed by contingency table methods, except for age at operation for which the Kruskal–Wallis test was used. Comparisons of cumulative incidence of local recurrence were made using Cox's proportional hazards model. In the multivariate analyses adjustment was made for age, sex, type of operation and Dukes' stage. A test of interaction between radiotherapy and the location of the tumour was also performed.

Results

The patients were divided into three groups according to distance from the anus to the tumour (0–5, 6–10 and more than 10 cm). The tumour was located in the low rectum in 149 patients, in the mid rectum in 182 patients and in the upper rectum in 126 patients.

Clinical characteristics are shown in *Table 1*. As expected, there was a significant relation between the distance from the anus to the tumour and the type of surgery performed. In patients with low rectal tumours, anterior resection was performed in 11 per cent and abdominoperineal resection in 89 per cent. In patients with mid rectal tumours the corresponding figures were 41 and 59 per cent, and in patients with tumours in the upper rectum 90 and 10 per cent. There were no significant differences between the three groups of patients with regard to age, sex, tumour stage and proportion randomized to radiotherapy plus surgery *versus* surgery alone.

In all, 37 (25 per cent) of 149 patients with tumour in the low rectum had a local recurrence compared with 34 (19 per cent) of 182 with tumour in the mid rectum and 17 (13 per cent) of 126 with tumour in the upper rectum. However, these differences were not statistically significant ($P = 0{\cdot}08$, test for trend).

The effect of radiotherapy on local recurrence rate, in relation to tumour distance from the anus, is shown in *Table 2*. Radiotherapy reduced the local recurrence rate from 30 to 20 per cent (relative reduction 33 per cent) in low rectal cancer, from 25 to 11 per cent (relative reduction 56 per cent) in mid rectal cancer, and from 21 to 5 per cent (relative reduction 75 per cent) for tumours in the upper rectum. The effect of radiotherapy was statistically significant for tumours in the mid and upper rectum but not for tumours in the low rectum (*Table 2*). However, the test of interaction between radiotherapy and tumour distance from the anus was not significant ($P = 0{\cdot}26$).

Table 1 Clinical characteristics of patients operated for cure in the Stockholm II Trial in relation to tumour distance from the anus

	Tumour distance from the anus		
	≤ 5 cm (*n* = 149)	6–10 cm (*n* = 182)	> 10 cm (*n* = 126)
Median age (years)	69	68	69
Sex*			
Male	95 (64)	105 (58)	74 (59)
Female	54 (36)	77 (42)	52 (41)
Dukes' stage*			
A	55 (37)	66 (36)	46 (37)
B	48 (32)	53 (29)	41 (33)
C	46 (31)	63 (35)	39 (31)
Operation*			
Anterior resection	16 (11)	75 (41)	113 (90)
Abdominoperineal resection	133 (89)	107 (59)	13 (10)
Radiotherapy*			
Yes	76 (51)	80 (44)	60 (48)
No	73 (49)	102 (56)	66 (52)
Local recurrence			
No. of patients*	37 (25)	34 (19)	17 (13)
Hazard ratio†	1·0	0·7 (0·4–1·2)	0·5 (0·3–1·1)

Values in parentheses are *percentages or †95 per cent confidence intervals

Table 2 Adjusted effects of preoperative radiotherapy on local recurrence in relation to tumour distance from the anus

Distance from the anus	Proportion of patients with local recurrence*			
	No radiotherapy	Radiotherapy	Hazard ratio†	*P*
≤ 5 cm	22 of 73 (30)	15 of 76 (20)	0·7 (0·4–1·4)	0·3
6–10 cm	25 of 102 (25)	9 of 80 (11)	0·4 (0·2–0·9)	0·03
> 10 cm	14 of 66 (21)	3 of 60 (5)	0·2 (0·1–0·7)	0·01

Values in parentheses are *percentages or †95 per cent confidence intervals

Discussion

Local recurrence after surgical treatment of rectal cancer is an important clinical problem. Several factors that adversely influence the risk of local recurrence have been identified[14,19–23]. These include tumour characteristics such as tumour stage, grade of differentiation, lymphatic, venous or perineural invasion, circumferential margin involvement and fixation in the pelvis. Several studies have also reported a higher risk of local failure in patients with tumours in the low rectum, which presumably is related to an impaired ability to excise widely in the depths of the pelvis[24].

The rationale for using radiotherapy in rectal cancer is the ability of irradiation to eradicate tumour cells in the periphery of the tumour where the tumour cell deposits are small and well vascularized. It may be postulated that radiotherapy is more efficient if excision of a tumour with wide surgical margins is difficult owing to inaccessibility, as in the pelvis, than it is if the excision can be performed with adequate margins. Accordingly, it has been suggested that preoperative radiotherapy should mainly be used in low rectal cancer, especially if an abdominoperineal excision is planned[24,25]. In the present study there was an increased risk of local recurrence for tumours in the lower rectum compared with tumours in the upper rectum but the difference was not statistically significant.

Preoperative radiotherapy reduced the local recurrence rate irrespective of the tumour distance from the anus. Surprisingly, the reduction was larger, both in terms of absolute and relative reduction, for tumours in the upper rectum than for tumours in the lower rectum. However, the difference in hazard ratios between the three groups of patients was not statistically significant according to the test of interaction. The lack of statistical significance may be due to an insufficient number of events in each group, but it cannot be concluded that the effect of radiotherapy is different for tumours at different levels in the rectum, implying that patients with cancer in the upper and mid rectum should also be considered for preoperative radiotherapy.

The results of this study may be related to the fact that when the Stockholm II Trial was performed almost all patients with rectal cancer had surgery with conventional techniques, that is blunt dissection of the rectum with a high proportion of abdominoperineal resections. With this technique the mesorectum may easily be damaged with subsequent spread of tumour cells or microscopic tumour deposits in the pelvis. If the number of residual tumour cells is large, radiotherapy may be less effective than if the number of residual tumour cells is small. With conventional dissection the upper mesorectum is usually better preserved than the lower mesorectum, which is more often torn.

With the technique of total mesorectal excision (TME), which involves specimen-orientated surgery by sharp dissection under direct vision in place of conventional manual extraction techniques, an intact mesorectum can usually be excised[26,27]. Accordingly, the local recurrence rate has been significantly reduced not only in single dedicated centres but also in a population-based study from Stockholm and in other population-based series[28–30].

Most centres using the TME technique have not used preoperative radiotherapy and the significance of this adjuvant treatment in combination with TME surgery has not yet been established. However, in a Swedish study, only three (2 per cent) of 196 patients who were treated with a combination of TME surgery and preoperative radiotherapy had a local recurrence within 2 years of follow-up, compared with 11 (9 per cent) of 122 patients treated with TME surgery alone[28].

In conclusion, the results of this study imply that preoperative radiotherapy plays an important role in rectal cancer, irrespective of the location of the tumour, when conventional surgical techniques are used. To irradiate only patients with tumours in the lower rectum and to omit this treatment for patients with tumours in the mid and upper rectum cannot be recommended. Whether this statement is valid with standardized TME surgery is not known. The ongoing Dutch trial[31], evaluating TME surgery with or without preoperative radiotherapy, may help to answer this question. Until this knowledge is available, current indications for preoperative radiotherapy should also be used for TME surgery.

Acknowledgements

The study was supported by Jerzy och Eva Cederbaums Minervafond and The Cancer Society in Stockholm. The authors thank the members of the Stockholm Colorectal Cancer Study Group for supplying data and Toom Singnomklao for help with the collection of data.

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Original article

Long-term results of treating hepatic colorectal metastases with cryosurgery

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Background: The purpose of this study was to determine the long-term efficacy of cryosurgery as an adjunct to hepatic resection in patients with colorectal liver metastases not amenable to resection alone.
Methods: Thirty patients met the following inclusion criteria: metastases confined to the liver and judged irresectable, ten or fewer metastases, cryosurgery alone or in combination with hepatic resection allowed tumour clearance.
Results: Median follow-up was 26 (range 9–73) months. Overall 1- and 2-year survival rates were 76 and 61 per cent respectively. Median survival was 32 months. Disease-free survival at 1 year was 35 per cent, at 2 years 7 per cent. Six patients developed recurrence at the site of cryosurgery; given that the total number of cryosurgery-treated lesions was 69 the local recurrence rate was 9 per cent.
Conclusion: In patients with colorectal liver metastases, local ablative techniques can be used as an effective adjunct to hepatic resection to obtain tumour clearance.

Paper accepted 3 January 2001

British Journal of Surgery 2001, **88**, 844–849

Introduction

Hepatic metastases are the main cause of death in patients with colorectal cancer[1]. In patients with metastatic disease confined to the liver, resection offers the best chance of cure. After resection, a 5-year survival rate of 35 per cent can be achieved[2–7]. However, only a minority (10–15 per cent) of patients with liver metastases is suitable for resection. Resectability is usually determined by the absence of extrahepatic disease, a maximum of four liver deposits and the ability to obtain free resection margins[8]. Recently, it has been demonstrated that the presence of more than four metastases does not automatically preclude resectability[5,9–11]. Liver resection in patients with more than four metastatic lesions has been shown to result in a 5-year survival rate of 25 per cent as long as resection margins are free of tumour[5]. In patients with more extensive disease, however, it may be difficult to resect all tumour tissue adequately. It is in this group of patients that local tumour ablative techniques such as cryosurgery can be used as an adjunct to hepatic resection[12,13]. Using cryosurgery, liver deposits are frozen with the aid of liquid nitrogen circulating through a probe placed in the centre of the tumour[14]. The method has been shown to be safe and to allow treatment of one or more liver metastases[12,13,15–24].

The aim of this study was to describe the long-term results of cryosurgery when used either alone or in combination with liver resection in patients with colorectal liver metastases.

Patients and methods

Patient selection

Patients with documented colorectal liver metastases who met the following criteria were considered for cryosurgery: metastases confined to the liver; metastases judged irresectable due to technical considerations related to location or extent of the disease; less than 50 per cent of liver volume affected and the number of metastatic deposits no greater than ten; cryosurgery alone or in combination with resection would allow complete tumour eradication.

Previous chemotherapy was not considered an exclusion criterion. To determine the extent of the disease before operation, all patients underwent spiral abdominal computed tomography (CT), chest radiography or CT of the thorax, and more recently fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET). Barium enema or colonoscopy was performed to exclude local recurrence.

Liver function tests and determination of carcinoembryonic antigen (CEA) level were performed routinely.

Operative procedure

The operation was performed as a separate procedure through an extended right subcostal incision. The abdominal cavity was explored thoroughly to exclude extrahepatic disease. Suspicious lymph nodes or peritoneal deposits were subject to biopsy and fresh-frozen section. The extent of liver involvement was mapped out by careful palpation and intraoperative ultrasonography. The number of lesions and their relationships to major biliary and vascular structures were determined, and resectability was assessed. Tumour size and locoregional invasion of perihepatic structures were not considered a contraindication to operation as long as resection could clear all tumour tissue. In all cases surgical resection was considered the treatment of choice. When complete resection could not be achieved, patients were included in the study and the decision was taken either to perform cryosurgery alone or to combine resection of resectable lesions with cryosurgery of irresectable deposits.

Technique of hepatic cryosurgery

After localization of the liver metastases the cryoprobe was introduced under ultrasonographic guidance into the centre of the tumour. Cryosurgery was performed as described previously using an LCS 2000 apparatus (Candela, Eindhoven, The Netherlands)[12,23]. During the freezing process continuous ultrasonographic monitoring of the lesion was carried out to assure that the 'ice ball', visible as a hypoechogenic area around the tip of the cryoprobe, exceeded the diameter of the lesion by about 1 cm. The volume of tumour that can be frozen with one cryoprobe depends on the diameter of the probe. Cryoprobes with a diameter of 5 and 10 mm generally result in an ice ball of 4 and 6 cm respectively. By introducing more than one probe, an adequately frozen area with a diameter of 10 cm can be attained. The time of freezing was dependent on the production of an adequate ice ball, but generally one freeze period lasted for 20 min, followed by thawing for at least 10 min. Two freeze–thaw cycles were always performed per lesion.

Postoperative follow-up

Postoperative follow-up was obtained at 6 weeks and then every 3 months by assessment of CEA concentration and abdominal spiral CT. The first postoperative CT scan was used as a reference to evaluate liver recurrence. When indicated, additional investigations were performed to detect recurrence outside the liver. Regular follow-up was reduced to twice yearly after 2 years. When new liver deposits became evident, subsequent resection or cryosurgery was performed whenever possible. In case of doubt about recurrence at the site of cryosurgery, an ultrasonographically guided biopsy was performed. After cryosurgery, patients did not routinely receive chemotherapy. Chemotherapy was started only in cases of recurrence not amenable to resection or cryoablation.

Results

Patient and treatment characteristics

Between January 1994 and October 1999, 30 patients with irresectable liver metastases from colorectal cancer met the prospective criteria and underwent hepatic cryosurgery with or without additional hepatic resection. These patients represented 15 per cent of the cases surgically treated for colorectal liver metastases within the study interval. Sixteen patients had synchronous metastases, and 14 had metachronous metastases (*Table 1*). The median time from detection of liver metastasis to operation was 5·5 months. In seven patients this period was more than 1 year because of delay in primary referral. Eleven of the 30 patients were initially treated by chemotherapy before referral. By that time, eight patients showed progression of the disease, noted by enlargement of the liver deposits on CT. In these patients the median duration of chemotherapy was 10·5 months. A further eight patients developed metastases during adjuvant chemotherapy. Thus, a total of 16 patients had metastases that were progressive on chemotherapy at the time of operation.

The number of liver metastases per patient varied from 1 to 10 (median 3). The number of nodules per patient treated by cryosurgery ranged from 1 to 7 (median 2). The tumour and treatment characteristics of all patients are given in *Table 2*. Fourteen patients had four or more lesions, and 16

Table 1 Patient characteristics

No. of patients	30
Sex ratio (M : F)	19 : 11
Mean (range) age (years)	62 (45–79)
Synchronous : metachronous	16 : 14
Median (range) interval from diagnosis of primary tumour to detection of metachronous metastases (months)	12·5 (7–29)
Median (range) time from detection of metastases to cryosurgery (months)	5·5 (1–41)
Failure of chemotherapy before cryosurgery*	16 (53)
Median (range) follow-up (months)	26 (9–73)

*Value in parentheses is a percentage

Table 2 Tumour and treatment characteristics

	No. of metastases		Size of metastases		Size of cryo-treated metastases	
	< 4	≥ 4	< 4 cm	≥ 4 cm	< 4 cm	≥ 4 cm
No. of patients	16	14	9*	21*		
Patients treated by cryosurgery only	4	3	1	6		
Patients treated by cryosurgery plus resection	12	11	8	15		
No. of lesions treated			82†	33†	47	22

*Number of patients according to the size of the largest metastatic lesion; †number of lesions according to size

had fewer than four metastases. Seven patients were treated by cryosurgery alone. In all other cases cryosurgery was combined with resection of the resectable lesions. Of 115 metastases, 69 (60 per cent) were treated by cryosurgery.

The size of the metastases varied from 1 to 18 cm, with a maximum diameter of the cryosurgery-treated lesions of 9 cm. Most lesions treated by cryosurgery were less than 4 cm in diameter.

Three patients underwent repeat cryosurgery for recurrent liver metastases. One patient was treated twice for recurrence; thus the total number of cryosurgical procedures was 34. Median follow-up after cryosurgery was 26 months, and the median follow-up after detection of metastases was 40 months.

Mortality and morbidity

There was one postoperative death from acute myocardial infarction 14 days after an uncomplicated cryosurgical procedure. The morbidity rate associated with the 34 procedures was 26 per cent. Haemorrhage from a cryosurgery-treated lesion was encountered twice. One patient had to be returned to the operating room because of haemorrhage; another required packing of the liver during the procedure due to hepatic cracking of the ice ball with associated haemorrhage. Four patients developed an abscess of the cryosurgery-treated area. All were treated by percutaneous drainage. Three patients developed pneumonia after the procedure. Right pleural effusion was observed in most patients, probably due to the irritative process beneath the diaphragm. Total operating time varied from 2 to 6 h. The median hospital stay for the 34 procedures was 10 (5–106) days.

Survival

At a median follow-up of 26 months, 14 patients had died, 13 from metastatic disease and one postoperative death. After cryosurgery the overall survival rate at 12 months was 76 per cent, and at 24 months it was 61 per cent (*Fig. 1*). Median survival was 32 (range 0·5–58) months. The 1- and 2-year survival rates after detection of the metastases were 83 and 68 per cent respectively. Median survival after detection of the metastases was 46 months. Patients with lesions smaller than 4 cm had an increased survival rate compared with those with lesions of 4 cm or more (*Fig. 2*). Median survival for patients with lesions smaller than 4 cm was 46 months, compared with 18 months for those with lesions of 4 cm or greater ($P < 0{\cdot}05$, log rank test). No significant correlation was found between the number of metastases and survival.

At time of follow-up 25 of the 30 patients had developed recurrent disease. The disease-free survival rate at 1 year was 35 per cent, and that at 2 years was 7 per cent. The median time to detection of recurrence was 7 months. Of the 25 patients with recurrent disease, 18 patients presented with hepatic recurrence. In 11 cases the liver was the only site involved. Extrahepatic recurrence was observed in 14 cases: lungs (six), colon and/or rectum (three), other (nine). Six patients developed local recurrence at the site of cryosurgery. In four of these patients the cryo-treated lesion was situated close to the portal bifurcation or inferior vena cava. In two of these cases there was some doubt during the procedure concerning the radicality of the freezing process. With regard to the total number of cryosurgery-treated lesions ($n = 69$) in the series, the local recurrence rate was 9 per cent. Three local recurrences occurred in tumours of 4 cm or more in diameter.

Discussion

In only a minority of patients are colorectal liver metastases amenable to resection. Most patients have widespread liver involvement or extrahepatic disease which precludes any surgical approach. However, in a well defined subgroup of patients with irresectable tumours, complete tumour clearance of the liver can be achieved by cryoablation of the liver metastases with or without combined resection of resectable lesions. This study has shown that an aggressive approach is rewarding in a selected group of patients and

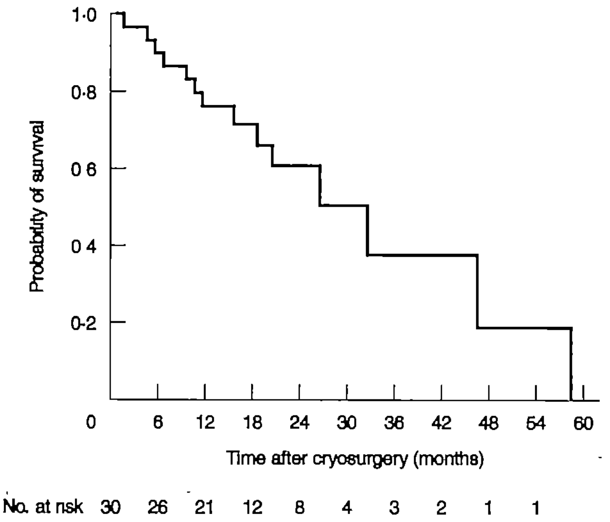

Fig. 1 Kaplan–Meier curve of survival after cryosurgery

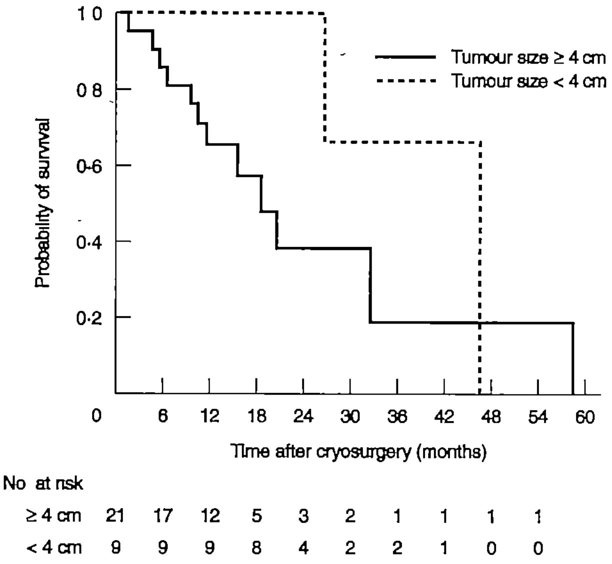

Fig. 2 Kaplan–Meier survival curves after cryosurgery in relation to the size of metastases. $P < 0{\cdot}05$ (log rank test)

can result in significant prolongation of survival. Median survival was 32 months despite inclusion in the study of patients with progressive disease during chemotherapy. These results compare favourably to those of chemotherapy, for which a median survival of between 12 and 17 months has been reported, depending on the schedule used[25–28]. Nevertheless patient selection may have contributed to the superior results in the present series, particularly as patients selected for this study had a limited number of metastases (no more than ten) and no extrahepatic disease.

This study concurs with other studies on cryosurgery of colorectal liver metastases. In these series the 1-year survival rate varied from 72 to 88 per cent, while 2-year survival rates of between 52 and 72 per cent have been reported[12,13,15,16,19,20,24]. As in the present study, cryoablation of irresectable lesions was generally combined with resection of those lesions that were amenable to operation. The use of cryosurgery in combination with additional resection of resectable lesions increases the applicability of the method, especially in patients with a combination of large lesions and small deposits[24]. As cryoablation seems to be less reliable for large metastases, resection is to be preferred for larger lesions and cryoablation for irresectable smaller lesions. Adam *et al.*[12] and Seifert and Morris[19] reported that overall survival is significantly better in patients in whom the maximum diameter of the cryo-treated lesion is smaller than 3 cm. Temperatures reached at the edge of large lesions may be inadequate unless several cryoprobes are used in the same lesion.

Of all lesions treated by cryosurgery, the overall local recurrence rate at the cryosurgical site was 9 per cent. This value for local recurrence is low in comparison with a local recurrence rate of 44 per cent described by Adam *et al.*[12]. However, others have also reported local recurrence rates at the cryosurgical site as low as 2·5 and 9 per cent[15,17]. Inadequate freezing was observed mainly in patients with lesions situated close to the inferior vena cava or portal bifurcation, owing to the heat sink effect of the high blood flow. Four patients with local recurrence at the cryosurgical site had tumour situated close to these large vessels. Only two local recurrences were observed in lesions treated at other sites.

In this study the overall disease-free survival rate at 1 year was 35 per cent. Most patients developed liver recurrence outside the cryo-treated area, or presented with extrahepatic recurrence. These findings are in agreement with those of other series, which report disease-free survival rates varying from 15 per cent at 15 months to 29 per cent at 24 months[12,15,17,22,23]. In contrast to several other series, routine postoperative chemotherapy was not used in the present study, although several series have reported significant benefit from this approach[12,19]. In a series of 116 patients treated by cryosurgery combined with intra-arterial chemotherapy, Seifert and Morris[19] observed a 2-year survival rate of 56 per cent, while an earlier report mentioned a 2-year survival rate of 13 per cent in patients without intra-arterial chemotherapy[18]. Most patients in the present series, however, developed combined hepatic and extrahepatic recurrence, which would make a case for combined intra-arterial and systemic chemotherapy after cryoablation. Although postoperative chemotherapy after liver surgery for colorectal metastases continues to be controversial[29], recent data from Kemeny *et al.*[30] suggest a potential benefit of postoperative chemotherapy by the combined administration of intra-arterial floxuridine and systemic 5-fluorouracil–leucovorin.

Cryoablation of liver metastases may be considered a safe procedure[12–24]. The main complication in this series was abscess formation near the cryo-treated area. In all cases percutaneous drainage could be performed. The length of postoperative hospital stay related mainly to the extent of the accompanying hepatic resection.

In patients with a limited number of irresectable colorectal liver metastases, local cryoablation may be an attractive alternative to chemotherapy. Local tumour destruction should be considered as a complement to hepatic resection in order to obtain complete tumour clearance of the liver. Recently, radiofrequency ablation has emerged as a new therapeutic option for local destructive therapy of liver metastases[31,32]. This treatment should, likewise, be considered complementary to hepatic resection. However, with more widespread use of local tumour destructive techniques, randomized trials to compare chemotherapy with an aggressive surgical approach should be initiated in order to judge the potential benefit of local tumour destruction in patients with irresectable colorectal liver metastases.

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Follow-up confirms sustained benefit of circumferential stapled anoplasty in the management of prolapsing haemorrhoids

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Background: Circumferential stapled anoplasty is gaining popularity as a safe and effective treatment in the surgical management of haemorrhoids and mucosal prolapse. However, little is known about the medium- and long-term durability of this procedure. The aim of this study was to evaluate the medium-term results of stapled anoplasty in maintaining symptom remission and to identify possible procedure-related adverse effects.

Methods: Of a consecutive series of 85 stapled anoplasties in 83 patients, 64 patients were eligible for 6-month review; 50 patients were seen in surgical outpatient clinics and seven were contacted by telephone. All patients attending the outpatient clinic were questioned about current symptoms and overall satisfaction with the procedure. The staple line was palpated digitally and inspected at proctoscopy.

Results: Median (interquartile range) symptom scores were 6 (5–8) before operation compared with 0 (0–1) at 6 months ($P < 0{\cdot}01$). There was no deterioration in symptoms between 6-week and 6-month follow-up. No recurrences and no procedure-related adverse effects, in particular impaired continence or persistent anal pain, were identified.

Conclusion: The initial promising results of circumferential stapled anoplasty in effectively treating haemorrhoidal symptoms appear to be sustained at 6-month follow-up.

Paper accepted 11 February 2001

British Journal of Surgery 2001, 88, 850–852

Introduction

Circumferential stapled anoplasty may offer a safe and cost-effective alternative to conventional excision–ligation procedures in the management of prolapsing haemorrhoids. Published randomized controlled trials[1,2] suggest that the procedure is less painful than conventional surgery with many operations being carried out on a day-case basis. Earlier return to work may also be possible[3], with potential benefits both to the individual and society in general. Reduced bed occupancy may lessen the economic burden on an already overstretched health service.

Initial results of this longitudinal study of circumferential stapled anoplasty in the surgical management of patients with haemorrhoids and mucosal prolapse have been reported previously[3]. Data from randomized controlled trials and this prospective longitudinal study support the contention that the stapled procedure results in less postoperative pain and permits a more rapid return to normal activity than conventional excisional surgery. Long-term monitoring of patients undergoing this procedure is essential to assess its sustained safety and efficacy. In view of the relative novelty of circumferential stapled anoplasty, close follow-up of patients has been continued, both to confirm that the short-term benefits of symptom relief are sustained and to evaluate any potential procedure-related sequelae.

Patients and methods

Eighty-five procedures have been carried out in 83 patients over 2 years. Two patients, operated on early in the series with a conventional staple gun (CDH 33; Ethicon, Bracknell, UK), complained of persistent symptoms at 6-week follow-up and required a repeat stapling procedure for residual haemorrhoids. Sixty-four patients were eligible for 6-month follow-up. Patients were reviewed on an outpatient basis where possible, and a formal staple-line

Table 1 Symptom severity score rating system

Symptom severity score	Pain	Pruritis	Prolapse	Bleeding	Soiling	Incontinence to gas
0	None	None	Never	Never	Never	Never
1	Only with stool	Occasionally	With straining	Spotting	Mucus discharge	Occasional
2	Constant pressure	Permanent	Permanent	Dripping into pan	Occasional soiling	No control
3				Without stool	Incontinent	
4				Staining underwear		

Maximum possible score 15

examination was carried out. Patients who did not attend on two occasions were contacted by telephone. Symptom assessment and scoring was carried out using the standard symptom scoring method described previously (*Table 1*)[3]. Patients were questioned about their overall satisfaction with the procedure and regarding any possible adverse symptoms related to continence, urgency or unsatisfactory defaecation. Digital rectal examination and proctoscopic examination were carried out to assess any residual haemorrhoidal tissue or prolapse, with particular attention to the presence of residual staples or staple-line stenosis.

Results

Of 64 patients eligible, 57 were followed up at 6 months. Fifty patients (88 per cent) were seen at outpatient clinics and seven (12 per cent) were contacted by telephone. Seven patients were lost to 6-month follow-up owing to relocation, but all had been satisfied with the operation at the 6-week review. Of the 57 patients followed up at 6 months, all expressed high levels of satisfaction with the symptomatic results of the procedure. None required further treatment for procedure-related complications.

Median (interquartile range) symptom scores were 6 (5–8) before operation and 0 (0–1) at 6 months ($P < 0{\cdot}01$; Wilcoxon rank test). Symptom scores did not change significantly between 6-week and 6-month follow-up (*Fig. 1*). Forty-two patients (74 per cent) had a symptom score of 1 or less. None of the 50 patients examined had staple-line stenosis. There was no restenosis in the two patients found to have stenosis at 6 weeks. Residual staples were present in six of the 50 patients examined, but only one patient was aware of staples on postdefaecation wiping. Examination revealed the presence of a low staple line. Although minor persisting anal skin tags were observed in two patients these did not give rise to symptoms. The most common residual symptoms seen at 6 months were minor bleeding ($n = 9$) and refractory pruritus ani ($n = 7$).

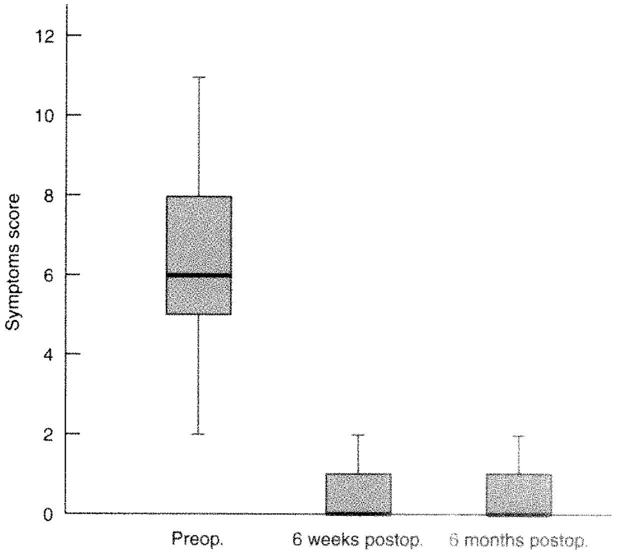

Fig. 1 Symptom severity scores for all patients before operation, and 6 weeks and 6 months after circumferential stapled haemorrhoidectomy. Horizontal bars, boxes and error bars represent median, interquartile range and range respectively

Discussion

Excisional haemorrhoidectomy has to date remained largely unchallenged as the operative treatment of choice for symptomatic prolapsing haemorrhoids[4]. The results are, however, variable with at least one series reporting a high incidence of recurrent symptoms at a median of 2·5 years after operation[5].

With the development of surgical stapling technology, stapled anoplasty is now a viable alternative procedure for haemorrhoidal prolapse and may offer a number of possible advantages with regard to reduced postoperative pain and a quicker return to normal activity. In determining the efficacy and cost effectiveness of any new procedure it is essential to demonstrate its durability in the resolution of haemorrhoidal symptoms. While initial experience of this technique has largely been promising there have been reports of immediate[6] and medium-term[7] complications. The data presented in this study demonstrate favourable medium-term results with sustained relief of haemorrhoidal symptoms in a large cohort of patients with no evidence of significant complications, in particular urgency or post-operative pain. More importantly, patients did not complain of deterioration or recurrence of symptoms compared with those reported at 6 weeks; indeed, there was a trend towards continuing improvement. These results do, however, show that chronic pruritus ani may persist despite adequate treatment of haemorrhoids and may merit referral to a dermatologist[8]. It is reassuring that the two cases of early anal stenosis did not recur.

There has been some debate regarding the aesthetic outcome for patients with a significant external cutaneous component who undergo the stapling procedure. Proponents of the conventional excision–ligation technique argue that the cutaneous component can be dealt with effectively by excision. In the original description of circumferential stapled anoplasty, Longo[9] argued that, by reducing haemorrhoidal prolapse, the external haemorrhoidal component regresses in the early postoperative period, eventually forming radial cutaneous folds. This hypothesis is supported by the current results in which 21 of 57 patients followed up had a significant external haemorrhoidal component, with only two patients mentioning palpable external skin tags at 6-month review.

In conclusion, follow-up of patients undergoing circumferential stapled anoplasty demonstrates that symptomatic improvement is sustained in the medium term. There have been no recurrences and no procedure-related adverse sequelae with regard to continence or urgency. Residual staples have been seen in a minority of patients but do not appear to be troublesome. Patient satisfaction with the procedure remains high. Although longer follow-up is required, the initial promise of this approach[10] in the surgical management of prolapsing haemorrhoids appears to be sustained.

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Original article

Endocoil magnetic resonance imaging quantification of external anal sphincter atrophy

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Background: Anal function depends on the integrity and quality of the sphincter muscles. The diagnosis of external anal sphincter atrophy on endocoil magnetic resonography has been associated with poor outcome from sphincter repair, although the imaging criteria for atrophy remain unclear.

Methods: Women with intact sphincters on endosonography and either normal (more than 60 cmH_2O) ($n = 9$) or low ($n = 16$) squeeze pressures had endocoil magnetic resonography and electromyography. The area and fat content of the external anal sphincter and puborectalis were measured on mid-coronal magnetic resonography and images were graded as showing normal, intermediate or advanced atrophy. The definition of the external anal sphincter on endosonography and the thickness of the internal anal sphincter were also assessed.

Results: Women with a normal anal squeeze pressure had a larger external anal sphincter cross-sectional area (mean(s.d.) 240(56) *versus* 193(62) mm^2; $P = 0{\cdot}01$) with a lower mean fat content (mean(s.d.) 23(4) *versus* 30(6) per cent; $P < 0{\cdot}001$) than those with low squeeze pressures. There was an overall correlation between squeeze pressure, cross-sectional area ($r = 0{\cdot}32$, $P = 0{\cdot}02$) and fat content ($r = -0{\cdot}51$, $P < 0{\cdot}001$). Patients with a thin (less than 2 mm) internal anal sphincter and/or a poorly defined external sphincter on endosonography were more likely to have atrophy (positive predictive value 74 per cent).

Conclusion: Potential endosonographic markers for external anal sphincter atrophy are suggested, and a visual scale for endocoil magnetic resonographic assessment has been validated.

Paper accepted 15 February 2001

British Journal of Surgery 2001, **88**, 853–859

Introduction

Trauma to the anal sphincter and its nerve supply during vaginal delivery is the most common cause of faecal incontinence in women[1]. Endosonography has become an accepted technique for selecting those with anal sphincter disruption who might be eligible for anterior anal sphincter repair. Anal sphincter repair has a favourable outcome in 60–80 per cent of patients[2–4], although the long-term success rate falls to 50 per cent[5]. Endosonographic evidence of restoration of an intact ring of external anal sphincter (EAS) has been associated with a good result[6–8], although this is not the only determinant of outcome. Manometric variables have not been shown to be useful[8,9], but evidence of pelvic floor nerve damage, inferring EAS atrophy, has been associated with a poor outcome[10–12]. Endocoil magnetic resonance imaging (MRI) has provided supporting evidence that atrophy is associated with a poor clinical outcome[13], suggesting that qualitative EAS imaging may be an important determinant of surgical outcome.

Atrophy of the EAS is considered to be the end result of denervation. The ultimate effects of denervation on striated muscle depend on axonal distribution, as well as on the extent and duration of nerve damage. Following denervation, individual muscle fibres either regain a nerve supply from the branching of adjacent intact axons, or undergo degeneration and atrophy with fatty replacement. Single-

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The Editors have satisfied themselves that all authors have contributed significantly to this publication

fibre electromyography (EMG) is the 'gold standard' for the diagnosis of atrophy, as an increased mean fibre density indicates that reinnervation, following denervation, has occurred. However, it is an uncomfortable procedure, with limited sampling which may be unrepresentative of the sphincter as a whole.

The EAS is clearly visible on MRI, as the low signal from striated muscle contrasts sharply with the surrounding bright fat. The bulk of the muscle is easy to appreciate on high-definition endocoil images. Most MRI reports of anal sphincter atrophy have been anecdotal[14,15]; only one has documented measurement of sphincter area[13]. No study has assessed fat replacement within the EAS, which may be an important aspect of atrophy. Furthermore, no diagnostic criterion for the imaging of EAS atrophy exists for either endosonography or MRI.

Imaging may be the only method available for assessing muscle quality before anal sphincter surgery. To determine what endosonographic or endocoil magnetic resonance variable might be of value, two groups of patients with intact anal sphincters have been investigated: a control group with constipation and physiologically normal anal sphincters, and a group with idiopathic faecal incontinence and manometrically weak anal sphincters. The appearances of atrophic and normal anal sphincters have been related to single-fibre electomyographic recordings, and predictive factors on endosonography and a scheme for quantifying atrophy on MRI are suggested.

Patients and methods

Women with an intact EAS on endosonography were selected for this prospective study. The study group ($n = 16$) consisted of women with faecal incontinence with a reduced maximal anal squeeze pressure (less than 60 cmH_2O). The control group ($n = 9$) was recruited from a group receiving behavioural retraining for constipation, who had a normal maximal anal squeeze pressure (greater than 60 cmH_2O). Ethics committee approval had been granted for the study and informed written consent was obtained.

All women had anal endosonography and endocoil MRI; 11 had successful single-fibre EMG, but five declined examination owing to the discomfort involved.

Anal manometry was performed using a station pull-through technique (0·5-cm stations) with a radially arranged eight-channel, water-perfused (0·5 ml/min) manometry catheter. The mean maximal resting pressure and mean incremental squeeze pressures were measured (Medical Measurement Systems, Enschede, The Netherlands).

Anal endosonography

Anal endosonography was performed using a 3535 ultrasound scanner with a 10-MHz transducer (B&K Medical, Sandhoften, Denmark). During each examination, an image at the most cranial level of the anal canal where the EAS first formed a complete anterior ring was captured digitally on to a personal computer for subsequent blinded image analysis. The thickness of the internal anal sphincter (IAS) was measured at 3 and 9 o'clock, and the mean was recorded.

The images were assessed independently by two of the authors (A.B.W., C.I.B.) to ascertain whether the EAS was well defined or not. The reflectivity of the EAS is variable in women, but its thickness is demarcated (*Fig. 1a*) by an interface reflection on the inner border, between the EAS and the longitudinal muscle layer, and one on the outer border from a layer of subadventitial fat. The inner interface reflection was invariably visible. The EAS was considered poorly defined if the muscle layer was not clearly visible owing to loss of the outer interface reflection and/or poor differentiation between the reflectivity of the sphincter and perirectal fat (*Fig. 1b*).

Single-fibre electromyography

Single-fibre recordings were made in the EAS on the left and right sides at 3 and 9 o'clock using the Dantec Keypoint portable system Version 2 (Dantec Electronics,

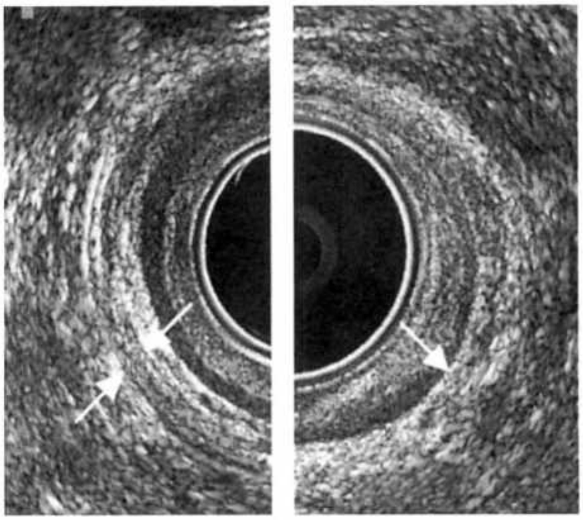

a Well defined EAS **b** Poorly defined EAS

Fig. 1 Definition of the external anal sphincter (EAS) on endosonography. **a** Well defined muscle layer and interface reflections (arrows). **b** Poorly defined with only an inner interface reflection visible (arrow)

Tonsbakken, Denmark), using a single-fibre needle[16] with a recording area of 25 μm. Each woman was positioned in the left lateral position and recordings were obtained using a technique described previously[17]. All potentials detected were saved on the computer for subsequent blinded measurement of mean fibre density. The procedure was abandoned when no potential was recorded after 15 min. Data were analysed using an established technique[18]. Traces were assessed independently by two of three blinded observers (A.B.W., D.M., T.N.). Normal mean fibre density in the EAS[19] in patients over the age of 50 years was assumed to be 1·37–1·79.

Endocoil magnetic resonance imaging

T2-weighted turbo spin-echo magnetic resonance images (time of repetition 3920, time of echo 120, six excitations, 256 matrix, slice thickness 3 mm, no gap, 22 slices, scan time 6 min 28 s) of the anal canal were acquired in axial and coronal planes, using a Philips 1·0-T magnet (Philips Medical Systems, London, UK) with a dedicated endoanal receiver coil housed in a carrier 19 mm in diameter. The coil was inserted into the anal canal with the patient in the left lateral position, the patient then turned supine, the coil stabilized between foam pads to reduce movement artefact, and the patient moved into the bore of the magnet.

During each study the coronal image corresponding the mid-anal canal level was selected. The imaging window was set at a width of 3000 and level of 800 that corresponded to pixel values for pure colour of black −700 and white 2300. Using the workstation image analysis software, blinded measurement of the cross-sectional area of the EAS on both sides was made by tracing the perimeter of each muscle, taking care not to include the longitudinal muscle. The maximum, minimum and mean pixel densities from within this area were recorded. The maximum value was considered to correspond to the signal from fat, and the minimum value to signal from striated muscle. From these values and the mean for the total sphincter area, a percentage fat content for the sphincter was calculated using a method described previously[20].

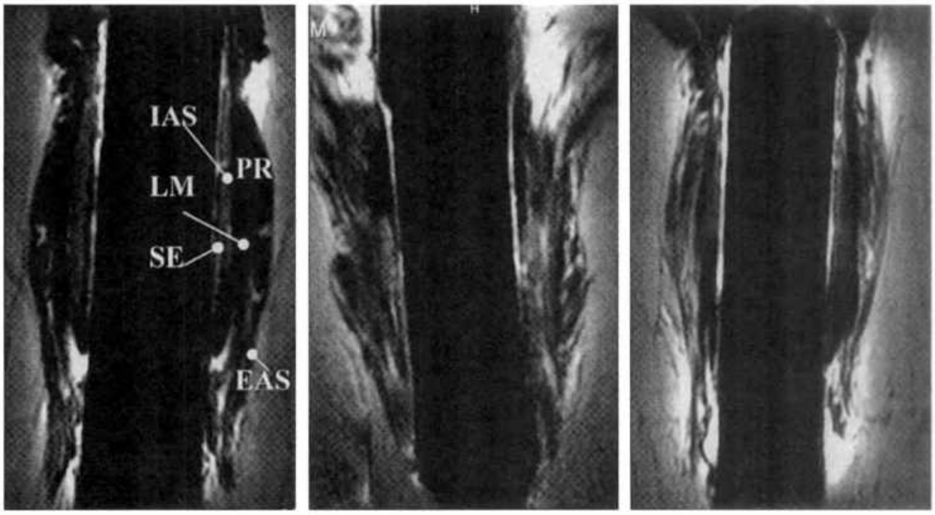
These measurements were time consuming and required a workstation. To assess whether visual assessment of the EAS on MRI correlated with these measurements, three coronal images were selected, of mean fibre density 1·75 (normal), 2·26 (increased; intermediate) and 2·85 (grossly increased; atrophic) (*Fig. 2*). These were used as templates to classify the remaining images.

Statistical analysis

The results are expressed as mean(s.d.) and an unpaired Student's *t* test used for analysis unless otherwise indicated.

Results

Five women declined EMG and in seven no potential was recordable (all in the reduced squeeze group). Recordings



a Normal **b** Intermediate **c** Advanced atrophy

Fig. 2 Mid-coronal endocoil magnetic resonance imaging templates for external anal sphincter atrophy. **a** Normal (mean fibre density 1·75). **b** Intermediate atrophy (mean fibre density 2·26). **c** Advanced atrophy (mean fibre density 2·85). EAS, external anal sphincter; IAS, internal anal sphincter; LM, longitudinal muscle; PR, puborectalis; SE, subepithelium

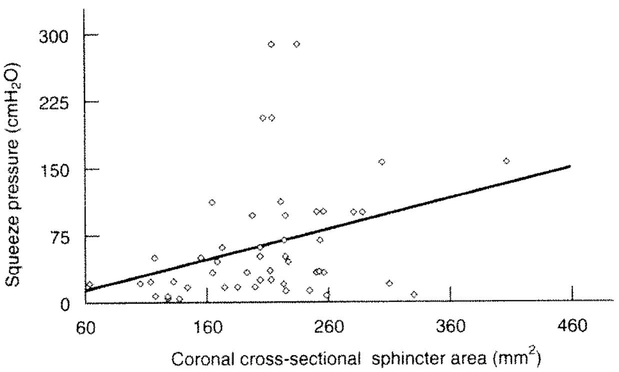


Fig. 3 Relationship between coronal cross-sectional external anal sphincter area and anal squeeze pressure

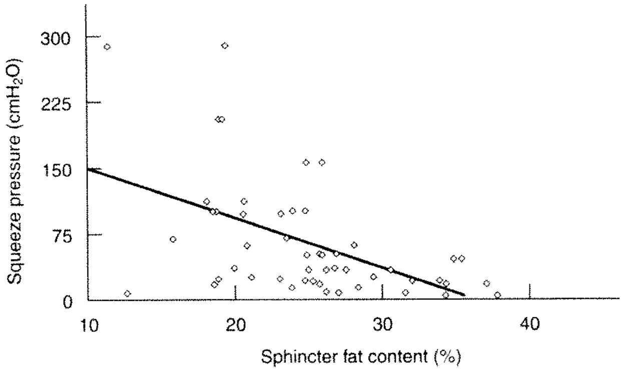


Fig. 4 Relationship between coronal cross-sectional external anal sphincter fat content and squeeze pressure

Table 1 Cross-sectional coronal external anal sphincter area, percentage fat content and squeeze pressure compared with magnetic resonance imaging grade

MRI classification	Squeeze pressure (cmH$_2$O)	EAS area (mm^2)	Fat content (%)
Normal	100(56)	248(55)	24(3)
Intermediate	65(92)	212(92)	30(6)‡
Advanced	21(11)*	158(11)†	29(5)§

Values are mean(s.d.). MRI, magnetic resonance imaging; EAS, external anal sphincter. *P = 0·001, †P = 0·003, ‡P = 0·017, §P = 0·013 *versus* normal group (unpaired Student's t test)

were impossible in two examinations owing to equipment failure. Eleven women had successful electromyographic assessment, bilateral in eight and unilateral in three.

Interobserver agreement for mean fibre density scoring was excellent with an intraclass correlation coefficient of 0·99 and minimal bias (0·001) between the two observers. The 95 per cent confidence interval of the mean of the differences between the two observers (0·026) was within the 95 per cent limits of agreement (– 0·24 to 0·21) for the mean of all the differences, indicating acceptable repeatability[21].

Women in the control group (n = 9) had a mean age of 55 (range 48–60) years compared with 62 (range 41–79) years for the study group (n = 16) (P not significant). The group with normal squeeze pressure had a significantly lower mean fibre density than those with reduced squeeze pressure (mean(s.d.) 2·16(0·41) *versus* 2·64(0·54); P = 0·04, non-paired t test). There was no correlation between maximum voluntary squeeze pressure and mean fibre density.

The mean cross-sectional external anal sphincter area on coronal MRI was greater in the normal squeeze group than the reduced squeeze group (240(56) *versus* 193(62) mm^2; P = 0·01). Women with a normal anal squeeze pressure had a lower sphincter fat content on MRI than those with a reduced anal squeeze pressure (23(4) *versus* 30(6) per cent; P < 0·001).

Anal squeeze pressure correlated with the cross-sectional anal sphincter area measured in the coronal plane (simple linear regression r = 0·32, P = 0·02) and sphincter percentage fat content (simple linear regression r = – 0·51, P < 0·001) (*Figs 3* and *4*). Larger sphincters contained less fat on MRI (r = – 0·3, P = 0·036).

Using the reference magnetic resonance images, the EAS was graded as normal in nine women, intermediate in eight and atrophic in eight. There was overall good agreement between the two observers (A.B.W., C.I.B.) (weighted κ = 0·78, P < 0·001); where disagreement existed a consensus was reached. A normal EAS showed a well defined muscle bulk with low fat content, an intermediate EAS had preservation of sphincter bulk but an increase in fat content, and an advanced atrophic EAS showed both a reduction in total muscle bulk and an increase in fat content (*Fig. 2*; *Table 1*).

The appearance of the EAS on MRI was related to the success rate for single-fibre EMG, as potentials were recorded in all eight women in the normal group, two of four in the intermediate group, but only one of six in the advanced group (P = 0·001, χ^2 test). In the three patients in whom EMG was recorded on one side only, the images confirmed unilateral EAS atrophy on the side concerned (*Fig. 5*).

There was excellent agreement between the two blinded observers (A.B.W., C.I.B.) for assessment of the visibility of the EAS on endosonography (*Fig. 1*) (κ = 0·91). Although there was no difference in cross-sectional area on MRI, fat content or squeeze pressures depending on whether or not

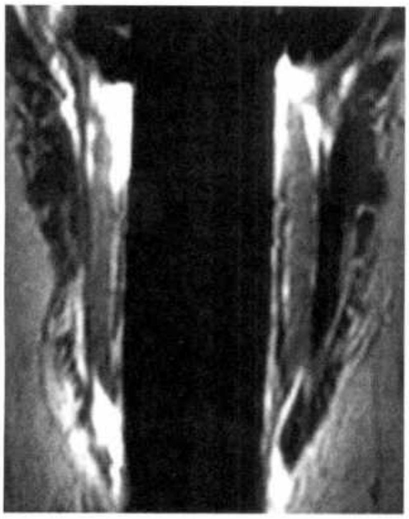


Fig. 5 Mid-coronal endocoil magnetic resonance image showing unilateral external anal sphincter (EAS) atrophy. It was not possible to record electromyographic potentials from the right side of the EAS. The mean fibre density of the left EAS was 3·5, indicating significant reinnervation

the EAS was clearly defined on endosonography, there was a relationship to the MRI grade. The EAS was not defined endosonographically in five of nine women with a normal EAS on MRI, five of eight women with an intermediate grade, and seven of eight women with advanced atrophy. The positive predictive value of poor endosonographic definition of the EAS on endosonography for predicting either intermediate or advanced atrophy on MRI was 71 per cent, with a negative predictive value of 50 per cent, sensitivity of 75 per cent and specificity of 44 per cent.

The IAS thickness on endosonography was less than 2 mm in all eight women with features of advanced atrophy on MRI, compared with four of eight in the intermediate group and five of nine in the normal group. The positive predictive value of a thin IAS on endosonography for predicting an abnormal grade on MRI (either intermediate or advanced) was 75 per cent, with a negative predictive value of 44 per cent (sensitivity 71 per cent, specificity 50 per cent). Combining both endosonographic criteria, i.e. the presence of a thin IAS and/or a poorly defined EAS, gave a positive predictive value of 74 per cent, with a negative predictive value of 67 per cent, sensitivity of 88 per cent and specificity of 44 per cent.

Discussion

An MRI endocoil classification of the EAS into normal, intermediate and advanced atrophy has been validated. The morphological differences between these are consistent with the known pathophysiology of EAS atrophy and were confirmed by direct EMG. The normal EAS comprises a dense, well defined muscle bulk with relatively little fat between muscle bundles. Denervation of striated muscle causes degeneration of individual muscle fibres[22], with fat replacement and an increase in fat content. The overall area of the EAS may be maintained, but an increased proportion of fat becomes apparent, as seen in the intermediate group. With more severe nerve damage further loss of muscle fibres leads to a reduced sphincter area, as seen in the advanced group (*Fig. 2*).

The choice of control group in this study may be criticized, as constipation has been associated with chronic straining and perineal descent[23]. Although no patient had clinical evidence of prolapse or excessive perineal descent, the mean fibre density for the group was 2·16, which is above normal for the age group. However, this should not invalidate the MRI classification of atrophy, and the normal template was based on a patient with a normal fibre density (1·75).

MRI of the EAS included the puborectalis muscle. This was consequent on using the coronal view, as in this plane it is impossible to separate the deep component of the EAS from the puborectalis. The axial view has been used[13], but in this study the entire anal sphincter area was measured, including the IAS. It was impossible to obtain reliable measurements of the EAS only in the axial plane, so a decision was made to use the coronal view. Although this included the puborectalis, which has a different terminal innervation from the EAS[24], the puborectalis may also become atrophic[25] and is important in the generation of squeeze pressure[26]. The appearances of EAS atrophy described are in keeping with previous reports[27,28]. Furthermore, in women in whom no electromyographic activity was recorded from one side of the sphincter, MRI independently showed EAS atrophy on the side concerned.

Denervation may also be assessed using transanal nerve stimulation to measure conduction in the terminal portion of the pudendal nerve[29]. Prolongation of pudendal nerve terminal motor latency is associated with idiopathic faecal incontinence, rectal prolapse, solitary rectal ulcer syndrome, severe constipation and sphincter defects[30–32]. However, prolongation of the pudendal nerve terminal motor latency may reflect damage to only the large, heavily myelinated nerve fibres[33], and it may be normal even in the presence of EAS atrophy[34,35]. The measurement of pudendal nerve conduction does not assess the innervation to the puborectalis, and it is impossible to record conduction latency on one side in up to 28 per cent of cases[36]. For these reasons only single-fibre EMG, which is accepted as the 'gold standard' for anal sphincter denervation, was performed in this study.

Assessment of EAS quality before surgery is desirable as it may predict outcome[13,37]. Squeeze pressure is not meaningful when the sphincter is torn, and EAS quality needs direct assessment by EMG or muscle biopsy[37], although both are liable to sampling error[38]. It may be difficult to obtain electromyographic recordings from an atrophic sphincter[33], which may explain a lack of correlation between fibre density and squeeze pressure[39]. In this study an inability to record potentials from the EAS was associated with EAS atrophy on MRI. In particular there were several women in whom the electromyographic potentials were recorded on one side only and MRI demonstrated unilateral EAS atrophy (*Fig. 5*), confirming the advantage that imaging has for assessing the entire anal sphincter.

The problem with using endosonography to assess EAS atrophy is that the outer border of the EAS is frequently poorly defined. Compared with MRI the differentiation between striated muscle and perirectal fat is much less precise. The slice thickness is also different: less than 1 mm on endosonography compared with 3 mm on MRI. A slight loss of muscle bulk may therefore have a more pronounced effect on the endosonographic definition of the EAS. Loss of definition of the outer border of the EAS on endosonography had a positive predictive value of 71 per cent for atrophy. Abnormal thinning of the IAS (less than 2 mm) has not been linked to striated muscle atrophy, but in the original study denervation was excluded only by normal pudendal nerve terminal motor latencies[40]. Briel *et al.*[13] measured the entire sphincter, including the IAS. The IAS is very easy to measure accurately on endosonography, and thinning was shown to have a positive predictive value of 75 per cent. This compares to a positive predictive value of 89 per cent for a purely visual assessment of EAS atrophy on MRI using histological confirmation[37].

The diagnosis of an EAS tear is most likely to be made using endosonography. If this also shows a thin IAS and/or a poorly defined EAS, endocoil MRI should be considered to determine whether the sphincter is grossly atrophic, as this may imply an unfavourable outcome from sphincter repair.

Acknowledgements

A.B.W. was funded by a research fellowship from the Royal College of Surgeons of England.

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Original article

Probability of axillary node involvement in patients with tubular carcinoma of the breast

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Background: The aim of this study was to investigate the frequency of axillary metastasis in women with tubular carcinoma (TC) of the breast.

Methods: Women who underwent axillary dissection for TC in the Western Sydney area (1984–1995) were identified retrospectively through a search of computerized records. A centralized pathology review was performed and tumours were classified as pure tubular (22) or mixed tubular (nine), on the basis of the invasive component containing 90 per cent or more, or 75–90 per cent tubule formation respectively. A Medline search of the literature was undertaken to compile a collective series (20 studies with a total of 680 patients) to address the frequency of nodal involvement in TC. A quantitative meta-analysis was used to combine the results of these studies.

Results: The overall frequency of nodal metastasis was five of 31 (16 per cent); one of 22 pure tubular and four of nine mixed tumours ($P = 0{\cdot}019$). None of the tumours with a diameter of 10 mm or less ($n = 16$) had nodal metastasis compared with five of 15 larger tumours ($P = 0{\cdot}018$). The meta-analysis of 680 women showed an overall frequency of nodal metastasis in TC of 13·8 (95 per cent confidence interval 9·3–18·3) per cent. The frequency of nodal involvement was 6·6 (1·7–11·4) per cent in pure TC ($n = 244$) and 25·0 (12·5–37·6) per cent in mixed TC ($n = 149$).

Conclusion: A case may be made for observing the clinically negative axilla in women with a small TC (10 mm or less in diameter).

Presented at the Third Leura International Breast Cancer Conference, Blue Mountains, New South Wales, Australia, November 1996

Paper accepted 5 February 2001

British Journal of Surgery 2001, 88, 860–864

Introduction

Tubular carcinoma (TC) of the breast was described more than 130 years ago in the *Manuel d'Histologie Pathologique*[1]. Historically, TC has been regarded as rare, with a low incidence of axillary node metastasis[2–5]. More recently, however, owing to the mammographic detection of smaller breast lesions and the increased awareness of TC by pathologists, the prevalence has increased. In a series of 107 patients with impalpable, mammographically detected lesions, the prevalence of TC was 27 per cent[6].

Despite the generally accepted view of infrequent nodal metastasis, considerable debate continues regarding the precise nodal frequency and the implications of routine axillary treatment for TC. The aims of this study were to investigate the incidence of axillary metastasis, based on a centralized pathological review of TC treated in Western Sydney and an assessment of the published literature, and to make recommendations regarding routine axillary treatment.

Patients and methods

Between January 1984 and December 1995 at Westmead Hospital and between February 1993 and December 1995 at BreastScreen Western, Parramatta, in the Western Sydney area of New South Wales, 56 women with TC of the breast were identified from computerized databases.

Individual records were studied and the following details recorded: patient characteristics, methods of detection and diagnosis, patterns of treatment and axillary node status. The tumour was detected by mammographic screening in approximately one-third of the women; the remainder were symptomatic. The initial diagnosis was made by excision biopsy in two-thirds of the women and by fine-needle aspiration or core biopsy in the rest.

Locoregional treatment

Although treatment varied according to the individual surgeon and radiation oncologist managing each patient, the majority of women ($n = 44$) had breast-conserving surgery and axillary dissection followed by radiotherapy to the breast; five had conservative surgery only and seven had a total mastectomy. Treatment to the axilla included dissection (37 women), radiotherapy (12), and dissection and radiotherapy (one); six women had no axillary treatment.

Histopathology

TC was diagnosed by several different histopathologists during the study. Central histopathology review was undertaken of specimens from the 38 women who had axillary dissection, to determine the component of tubular formation as well as other tumour details. These included the presence of other invasive and non-invasive components such as ductal carcinoma *in situ* (DCIS), extensive intraduct component (EIC) and lymphatic or vascular invasion. EIC was designated to tumours containing 25 per cent or more *in situ* component within the invasive tumour as well as *in situ* component outside the tumour. Tumour size was measured off slide.

Tumours were defined as pure tubular if the invasive component of the tumour had grade I features and contained 90 per cent or more tubule formation as part of the invasive component. Tumours were designated as mixed tubular if they contained 75 per or more but less than 90 per cent tubule formation.

On the basis of central pathology review, 31 tumours were classified as either pure TC (22) or mixed TC (nine) and form the basis of this report. Comparisons between categories of TC were undertaken using the Fisher's exact test because of small numbers.

Literature review

A review of the literature was undertaken using Medline to identify all articles published in English between 1971 and 1998 that dealt with TC and the frequency of nodal metastases ($n = 19$). The reference lists of the identified papers were appraised to improve the coverage of the review. With the addition of the present series, 20 studies were available which yielded 26 groups for analysis categorized as pure or mixed TC, or both. If the tubular component as a proportion was not given, pure tubular was assumed to be 90 per cent or more tubular component; mixed tubular was assumed to be 75 per cent or more but less than 90 per cent tubular component. If neither pure nor mixed tubular was stated, the case series was considered to contain both, with a tubular component of 75 per cent or more. The exact binomial was used to compute the 95 per cent confidence intervals for the rate of node metastasis because of the small numbers of patients in many studies. A quantitative meta-analysis was used to combine frequency of nodal involvement in the studies. Fixed or random effects models were used as appropriate, and the method adapted to small numbers[7].

Results

The median age for the whole group was 51 (range 27–70) years; 20 women were either perimenopausal or postmenopausal (*Table 1*). The tumour characteristics and frequency of node involvement are summarized in *Tables 2 and 3*. The median size of the pure TCs was 10 mm compared with 13 mm for mixed TCs. Eighteen of the 31 women had associated DCIS, which was mostly classified as low grade.

Five of 31 women had positive axillary nodes, one of 22 with pure TC and four of nine with mixed TC ($P = 0{\cdot}019$, Fisher's exact test). Of the five women with nodal metastases, four had between one and three nodes involved (*Table 2*). *Table 3* shows the relationship between patholo-

Table 1 Characteristics of 31 women with tubular carcinoma of the breast

	Type of tubular carcinoma		
	Pure (n = 22)	Mixed (n = 9)	All (n = 31)
Age at diagnosis (years)*	51 (34–70)	50 (27–60)	51 (27–70)
Menopausal status			
Premenopausal	8	3	11
Perimenopausal	2	0	2
Postmenopausal	12	6	18
Side			
Left	10	4	14
Right	12	5	17
Presentation			
Symptomatic	14	7	21
Screen detected	8	2	10
Method of initial diagnosis			
Fine-needle or core biopsy	5	4	9
Excision	17	5	22

*Values are median (range). There were no statistically significant differences between patients with pure and mixed tubular carcinoma

Table 2 Clinical characteristics of 31 women with tubular carcinoma of the breast

	Type of tubular carcinoma		
	Pure ($n = 22$)	Mixed ($n = 9$)	All ($n = 31$)
Pathological size (mm)			
0–5	1	0	1
6–10	12	3	15
11–20	9	6	15
Median (range)	10 (5–17)	13 (8–20)	11 (5–20)
Presence of DCIS			
None	9	4	13
Low grade	12	5	17
Intermediate grade	1	0	1
Presence of EIC			
Yes	0	0	0
No	22	9	31
Lymphatic/vascular invasion			
Yes	0	1	1
No	22	8	30
Oestrogen receptor status*			
Positive	8	4	12
Negative	2	0	2
Positive axillary nodes	1†	4	
0	21	5	26
1–3	1	3	4
4–6	0	1	1

*Missing data owing to incomplete pathology reports. DCIS, ductal carcinoma *in situ*; EIC, extensive intraduct component. †$P = 0.019$ *versus* mixed tubular carcinoma (Fisher's exact test)

Table 3 Axillary node involvement by pathological tumour size and tubular component

	Proportion of patients with positive nodes		
Tumour size (mm)	Pure tubular	Mixed tubular	All
≤ 10	0 of 13	0 of 3	0 of 16
> 10	1 of 9	4 of 6	5 of 15
*P	0·409	0·167	0·018

*Fisher's exact test

gical tumour size, tubular component and the frequency of positive axillary nodes. None of the 16 women with a tumour diameter of 10 mm or less had axillary metastases compared with five of 15 with larger tumours ($P = 0.018$, Fisher's exact test).

The frequency of nodal involvement reported in 20 studies (including the present series) of TC published between 1972 and 1997, involving 680 patients, is summarized in *Table 4*. A wide range in the prevalence of nodal metastasis for patients with TC was reported. Much of this variation can be accounted for by the different histological criteria used to diagnose TC, as well as the inherent problems of small sample sizes in some studies. From the meta-analysis, the frequency of nodal involvement was 6·6 (95 per cent confidence interval 1·7–11·4) per cent for pure tubular lesions and 25·0 (12·5–37·6) per cent for mixed tubular cancers (those with a tubular component of 75 per cent or more and less than 90 per cent). In all studies (a mixture of both pure and mixed tubular cases) the frequency of node involvement was 13·8 (9·3–18·3) per cent.

Discussion

This study investigated the characteristics of 31 women with pure tubular or mixed tubular breast cancer who had undergone axillary dissection. The frequency of node metastasis was low which confirms the findings of many other publications (*Table 4*). The incidence of node metastasis was one of 22 for pure TC and four of nine for mixed TC. This difference was statistically significant. Of the five women with nodal metastasis, four had between one and three involved nodes, suggesting that when axillary metastases occur relatively few nodes are involved. This observation was also made by Winchester *et al.*[21] and Deos and Norris[16]. In the present study, the median size of mixed TC was larger (13 mm) than that of pure TC (10 mm), which is consistent with the results of other studies that have shown an increase in tumour size with a decrease in tubular proportion[9,15,18,20]. DCIS was present in 18 of 31 patients; low-grade DCIS was the most common, as reported previously[8–10,12,13,16,17,19,21,23].

Pathological tumour size is accepted as an independent factor in determining the frequency of node involvement[24,26–30]. The influence of TC size on axillary metastasis has been reported poorly, although Winchester *et al.*[21], using logistic regression analysis, showed that tumour diameter significantly influenced the incidence of node positivity. The present study confirmed this finding; none of the tumours with a diameter of 10 mm or less had node metastases. A possible explanation is that the proportion of less well differentiated components increases with the diameter of the TC. This hypothesis is supported by Linell and Ljungberg[20] and Peters *et al.*[15] who showed an increase both in tumour size and in frequency of node metastasis as the proportion of the tubular component in tumours decreased. In data presented from the Colorado tumour register by Leonard *et al.*[31] the findings differed. The overall rate of lymph node metastasis was lower in 209 patients with TC than in patients with ductal and lobular carcinomas. Even in tumours greater than 2 cm, the rate of positive axillary nodes was only 12 per cent. It was found, however, that among the small TCs (less than 1·0 cm) the rate of axillary nodal metastasis was similar (7–12 per cent). Whether these carcinomas were pure or mixed tubular was

Table 4 Frequency of axillary node metastases in published studies of patients with tubular carcinoma

Reference	Year	Tubular component (%)	Axillary dissection (*n*)	Positive nodes (*n*)	Percentage with node metastasis
Carstens *et al.*[2]	1972	≥ 75‡	35	3	8·6 (1·8–23·1)
Tobon and Salazar[8]	1977	≥ 75†	5	1	20·0 (0·5–71·6)
Carstens[9]	1978	≥ 90	14	1	7·1 (1·8–33·9)
		≥ 75 < 90	28	5	17·9 (6·1–36·9)
Feig *et al.*[10]	1978	≥ 90	15	0	0
		≥ 80 < 90	2	0	0
Cooper *et al.*[11]	1978	≥ 90	12	1	8·3 (0·2–38·5)
Oberman and Fidler[12]	1979	≥ 75	25	3	12·0 (2·6–31·2)
Eusebi *et al.*[13]	1979	≥ 75†	15	3	20·0 (4·3–48·1)
Lagios *et al.*[14]	1980	≥ 75	15	2	13·3 (1·7–40·5)
Peters *et al.*[15]	1981	≥ 90	16	0	0
		≥ 75 < 90	16	0	0
Deos and Norris[16]	1982	≥ 90	65	4	6·2 (1·7–15·0)
McDivitt *et al.*[17]	1982	≥ 75	109	12	11·0 (5·8–18·4)
Parl and Richardson[18]	1983	≥ 90	27	4	14·8 (4·2–33·7)
		≥ 75 < 90	39	15	38·5 (23·4–55·4)
Elson *et al.*[19]	1993	≥ 75	14	4	28·6 (8·4–58·1)
Linell and Ljungberg[20]	1980	≥ 90*	37	4	10·8 (3·0–25·4)
		≥ 75 < 90*	55	17	30·9 (19·1–44·8)
Winchester *et al.*[21]	1996	> 80	44	9	20·5 (9·8–35·3)
Leibman *et al.*[22]	1993	≥ 90	9	0	0
McBoyle *et al.*[23]	1997	≥ 90	22	1	4·5 (0·1–22·8)
Fein *et al.*[24]	1997	≥ 75‡	25	3	12·0 (2·6–31·2)
Moezzi *et al.*[25]	1996	≥ 90	5	0	0
Papadatos *et al.*	2001	≥ 90	22	1	4·6 (0·1–22·8)
		≥ 75 < 90	9	4	44·4 (13·7–78·8)
Meta-analysis					
All study groups (26)‡		≥ 75	680	97	13·8 (9·3–18·3)
Pure tubular groups (11)§		> 90	244	16	6·6 (1·7–11·4)
Mixed tubular groups (6)‡		≥ 75 or ≥ 80 and < 90	149	41	25·0 (12·5–37·6)

Values in parentheses are 95 per cent confidence intervals. *The tubular component as a proportion was not stated so pure tubular was assumed to be 90 per cent or more tubular component, and mixed tubular was assumed to be 75 per cent or more and less than 90 per cent tubular component. †Neither pure nor mixed tubular was stated so that the series was considered to contain both with a tubular component of 75 per cent or more. ‡Random effects model; §fixed effects model

not stated and, as has been shown in previous studies, this is essential information.

Based on the results of the present study and the meta-analysis, a strong case can be made for observing the undissected axilla of women with pure TC of 10 mm or less in diameter, thus avoiding the potential morbidity and the costs associated with either surgery or radiotherapy to the axilla. Axillary dissection is associated with a 10 per cent incidence of minor complications, including shoulder dysfunction, breast oedema, arm oedema, wound infection and seroma formation[24]. Similarly, irradiation of the axilla carries an equivalent risk of arm oedema. The decision whether or not to dissect or irradiate the clinically negative axilla is likely to become increasingly challenging as smaller breast lesions are detected mammographically. Owing to the commonly performed practice of day-case hookwire localization lumpectomy for impalpable, screen-detected tumours, and the evolving practice of large-core diagnostic removal of small tumours, clinicians will increasingly have to decide on further management of patients with a diagnosis of TC. For patients with a preoperative core biopsy diagnosis of TC, a one-stage wide local excision could be considered with observation of the axilla or alternatively a sentinel node procedure[32].

In conclusion, the risk of axillary involvement in women with pure tubular breast cancer is low (one of 22 in the present study), similar to that reported by other institutions. Based on this very low incidence, and the absence of nodal involvement in TCs of 10 mm or less, axillary observation is an acceptable therapeutic option in women with a clinically negative axilla and a small pure TC (10 mm or less). However, the diagnosis must be made using the strict histological criterion of more than 90 per cent tubule formation.

Acknowledgements

The authors acknowledge the assistance of Dr Lisa Tan with pathological review, Ms Linda Willis in identifying cases, Dr Greg Heard for editorial comment and Ms Cathie Lyons in preparation of the manuscript. The NSW Breast Cancer Institute receives financial support from the NSW Department of Health.

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Prediction of prognosis by echocardiography in patients with midgut carcinoid syndrome

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Background: The association between malignant midgut carcinoid tumours and right-sided cardiac lesions is well known, but the pathogenetic link between tumour secretion and valvular disease is still obscure. The purpose of this investigation was to describe the morphological and functional changes of valvular heart disease in a large patient series and to correlate these findings with hormonal secretion and prognosis.

Methods: Of 64 consecutive patients with the midgut carcinoid syndrome followed between 1985 and 1998, valvular heart disease was evaluated in 52 patients by two-dimensional echocardiography, Doppler estimation of valvular regurgitation and flow profiles. A majority was also evaluated with exercise electrocardiography and spirometry.

Results: Structural and functional abnormalities of the tricuspid valve were found in 65 per cent of patients, while only 19 per cent had pulmonary valve regurgitation. Long-term survival was related to excessive urinary excretion of 5-hydroxyindole acetic acid of over 500 µmol in 24 h, but the main predictor of prognosis was the presence of severe structural and functional abnormalities of the tricuspid valve. Although advanced tricuspid abnormalities were prevalent in this series, only one patient died from right ventricular heart failure.

Conclusion: Tricuspid valvular disease is a common manifestation of the midgut carcinoid syndrome and advanced changes are associated with poor long-term survival. Active surgical and medical therapy of the tumour disease reduced the hormonal secretion and, combined with cardiological surveillance, made right ventricular heart failure a rare cause of death in these patients.

Presented to the Millennium Meeting of Endocrine Surgeons, London, UK and Lille, France, May 2000
Paper accepted 19 February 2001
British Journal of Surgery 2001, 88, 865–872

Introduction

The association between cardiac valvular lesions and the midgut carcinoid tumour was independently reported by three groups in the 1950s[1–3]. Endocardial plaques of the cavities and the valves of the right ventricle were first ascribed to excessive secretion of serotonin (5-hydroxytryptamine; 5-HT) from liver metastases. The characteristic cardiac lesions seem to occur in more than half of patients with carcinoid syndrome[4–7]. A relatively small number of patients with left-sided cardiac lesions has been reported, mostly with combined patent foramen ovale or carcinoid lung tumours[8–10].

In the present report a large series of consecutive patients with the carcinoid syndrome observed over a prolonged period (1985–1998) is described in relation to clinical and echocardiographic characteristics at the time of first presentation. Fourteen patients were treated with potentially curative liver resection. Fifty patients were treated with octreotide for symptom palliation after resection of the primary tumour and regional metastases. Forty of these patients also underwent ischaemic therapy of liver metastases[11]. During the observation period 40 patients died, which allowed study of carcinoid heart disease in relation to 5-HT secretion, survival and cardiac morbidity.

Patients and methods

Study group

Over 10 years (1985–1994), 64 consecutive patients (mean(s.e.m.) age 61(4) (range 32–79) years; 35 women and 29 men) with midgut carcinoid syndrome were operated on (mean(s.e.m.) follow-up 85(8) months). During the first 2 years 12 patients were evaluated by cardiological examination only; thereafter echocardiography was performed in all patients before operation, so 52 patients in the study had non-invasive preoperative cardiac investigation. No patient had received chemotherapy before referral. The mean urinary 5-hydroxyindole acetic acid (5-HIAA) levels were raised more than tenfold at referral (mean(s.e.m.) 581(79) μmol per 24 h; reference level less than 50 μmol per 24 h).

Fourteen patients were treated with potentially curative liver resection after resection of the primary tumour, which resulted in a prolonged period of complete tumour remission without any medication. In this group, three patients have died (none from tumour-related disease) and the survivors have been followed for a mean(s.e.m.) of 128(10) months. Fifty patients had bilobar hepatic metastatic disease. After resection of the primary tumour and locoregional metastases, 40 of these patients underwent successive embolization of each hepatic artery 4–6 weeks apart. This was followed by octreotide treatment (median dose 200 μg). Repeat embolization was performed if there was objective evidence of tumour progression combined with symptoms and 5-HIAA levels were raised at least twofold. The follow-up programme included biochemical evaluation of tumour markers every 3 months, abdominal computed tomography every 6 months, and annual echocardiography and cardiological examination[11]. Twenty-seven of these 40 patients have died and surviving patients have been followed for a mean(s.e.m.) of 114(9) months. Ten patients were excluded from embolization therapy after primary surgery owing to other malignant diseases, poor general condition, liver cirrhosis, psychiatric disorder or reluctance to undergo further interventional therapy. The latter group of patients was treated medically with octreotide and all died during follow-up at a mean(s.e.m.) of 64(11) months[11]. In one patient with combined rheumatic and carcinoid valvular heart disease, tricuspid valve replacement with a mechanical prosthesis was performed.

Echocardiography

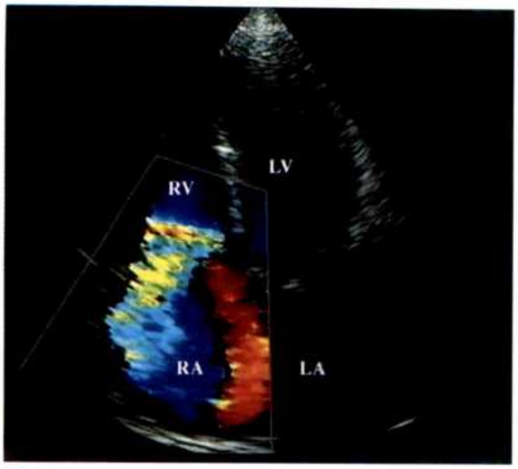
Two-dimensional echocardiography was performed before operation by means of an Acuson-128 XP echoscanner equipped with a 2-MHz transducer (Acuson Computed Sonography, Mountain View, California, USA). Patients were investigated in the left lateral position with optimal apical access through a mattress cut-out. Standard views, i.e. parasternal long- and short-axis, apical four-chamber, long-axis and two-chamber views, were obtained. In addition, a parasternal long-axis view of the right atrium and ventricle with optimal visualization of the tricuspid valve was obtained. The various views were recorded on to video tape. Right ventricular dimension was measured as the anteroposterior diameter in M-mode recording of the right and left ventricle. The latter was used for calculation of the ejection fraction by the cube formula. Structural abnormalities of the tricuspid valves (TSA) or pulmonary valves were graded (grade 0–4) depending on the severity of morphological changes (TSA grades: 0, no abnormality; 1, mild thickening or echo density; 2, moderate thickening; 3, severe thickening or moderate thickening combined with retraction; 4, severe thickening and retraction). The degree of tricuspid regurgitation (TR) was estimated by means of colour Doppler sonography (*Fig. 1a*) and continuous wave Doppler imaging as described previously[12] (*Fig. 1b*) (TR grades: 0, no abnormality; 0·5, transient not holosystolic regurgitation; 1, mild holosystolic regurgitation; 2, moderate; 3, severe; 4, extreme regurgitation). Pulmonary regurgitation (diastolic) was graded in a similar way. An index (TSA + TR) to describe the abnormalities of the tricuspid valve was derived by summation of these scores in the 52 patients. The diastolic function of the right ventricle was estimated as the atrial contraction to early peak filling (A/E) ratio of the diastolic Doppler flow. All echocardiographic evaluations were performed by one examiner (K.C.). TSA + TR scores of 1 or more were regarded as pathological.

Further cardiopulmonary tests

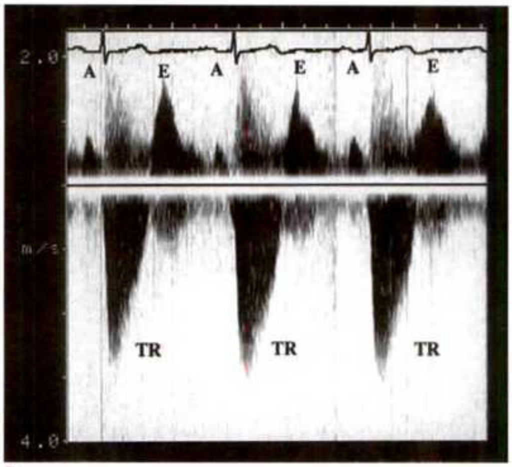
Exercise electrocardiography (ECG) was performed with a customized computerized system, giving reliable estimation of ST deviations in relation to time and heart rate as validated by Angelhed *et al.*[13]. Pulmonary function was assessed by spirometry. ECG at rest and clinical cardiac examination, including functional classification according to the New York Heart Association, were performed by one examiner (C.H.B.).

Statistical analysis

Data are expressed as mean(s.e.m.) unless otherwise stated. Survival data were calculated according to the Kaplan–Meier method. Comparisons were made with regard to excessive 5-HT secretion (urinary 5-HIAA levels in excess of 500 μmol per 24 h or not), and structural and functional abnormalities of the tricuspid valve (TSA + TR). In analysis of the risk ratio for death, univariate and stepwise regression tests were performed for age, sex, urinary excretion of 5-HIAA, systolic arterial blood pressure, left ventricular ejection fraction, TSA, TR, and TSA + TR. Student's *t* test was used in comparisons between groups. Repeated comparisons between groups were performed with analysis



a Echocardiography



b Continuous wave Doppler

Fig. 1 **a** Echocardiographic four-chamber view of the heart. Regurgitation of blood through the tricuspid orifice is shown by means of colour Doppler ultrasonography. RV, right ventricle; RA, right atrium; LV, left ventricle; LA, left atrium.
b Continuous wave Doppler recording of flow through the tricuspid valve, illustrating the diastolic early flow (E) and that resulting from atrial contraction (A). Tricuspid regurgitation (TR) during systole has in this case a maximum flow velocity of the order of 3 m/s, which corresponds to a pressure gradient of 36 mmHg between the right atrium and ventricle

of variance, and Fisher's exact test was used to compare proportions between groups. $P < 0{\cdot}05$ was regarded as statistically significant.

Results

Clinical characteristics

The mean observation time was 119(7) months in surviving patients and 63(11) months in those who died. The mean age at the time of diagnosis was significantly greater in non-survivors (64(2) years) than in survivors (56(3) years) ($P < 0{\cdot}02$). The clinical and cardiological data of the 52 patients who underwent echocardiographic investigations are given in *Table 1*. Hypertension (blood pressure greater than 150/90 mmHg or antihypertensive treatment) was more frequent in patients without tricuspid valvular disease than in patients with valvular disease (seven of 12 *versus* six of 40; $P = 0{\cdot}05$, Fisher's exact test). Fifty-six per cent of patients had normal findings on ECG. Abnormal ECG at rest was seen more frequently in patients without than in those with tricuspid valvular disease (seven of 12 *versus* 16 of 40) but the difference was not statistically significant (*Table 1*). The most common findings were ST-T wave abnormalities (13 per cent) and pathological Q waves (12 per cent).

Echocardiographic findings

The right ventricular dimensions were normal in all patients (*Table 1*). TSA (thickened, shortened, retracted or hypomobile valves resulting in incomplete coaptation) were found in 65 per cent and holosystolic TR was present in 65 per cent of patients (*Fig. 1*). The systolic gradient over the tricuspid valve was increased to 27(2) mmHg in patients with structural and functional abnormalities (*Table 1*). The structural–functional TSA + TR index was calculated and the mortality rate during follow-up increased significantly with the severity of tricuspid abnormalities ($P = 0{\cdot}02$, Fisher's exact test) (*Table 2*). The pulmonary valve did not reveal any structural abnormalities leading to pulmonary stenosis, but 19 per cent of all patients had holodiastolic pulmonary regurgitation (*Table 2*). The A/E ratio was significantly lower in patients with tricuspid valvular disease than in patients without valvular changes (1·01(0·05) *versus* 1·21(0·10); $P = 0{\cdot}05$). The left ventricular ejection fraction was also significantly lower in patients with tricuspid abnormalities (68(2) *versus* 75(3); $P < 0{\cdot}05$) (*Table 1*).

Urinary 5-hydroxyindole acetic acid excretion and tricuspid valvular disease

The 5-HIAA levels showed a progressive increase in relation to the severity of tricuspid valvular abnormalities subgrouped according to the TSA + TR scores. In patients with advanced tricuspid valvular disease (TSA + TR 4 and above) the urinary excretion of 5-HIAA was 901(196) µmol per 24 h *versus* 306(105) µmol per 24 h in patients with normal valves (*Table 2*).

Table 1 Clinical and cardiological characteristics of patients with the carcinoid syndrome

	All patients ($n = 52$)	No tricuspid valve disease ($n = 12$)	Tricuspid valve disease ($n = 40$)
Clinical			
Age at diagnosis (years)*	61(2)	63(3)	60(2)
Sex ratio (F : M)	31 : 21	9 : 3	22 : 18
Functional class (NYHA)*	1·4(0·1)	1·5(0·2)	1·3(0·1)
Systolic blood pressure (mmHg)*	142(3)	154(6)	138(3)
Hypertension†	13 (25)	7 (58)‡	6 (15)‡
Urinary 5-HIAA at referral (µmol per 24 h)*	545(84)	306(105)	635(91)
Pathological chest radiography findings†	6 (12)	0 (0)	6 (15)
Forced expiratory volume in 1 s (litres)*	3·0(0·2)	2·8(0·4)	3·0(0·2)
Follow-up (months)*	92(9)	107(22)	80(9)
Deaths†	32 (62)	6 (50)	26 (65)
From cardiovascular disease	8 (15)	3 (25)	5 (13)
From heart disease	5 (10)	2 (17)	3 (8)
Palliatively treated, alive†	11 (21)	3 (25)	8 (20)
Cardiological			
Ischaemic heart disease†	8 (15)	2 (17)	6 (15)
Pathological ECG at rest†	23 (44)	7 (58)	16 (40)
Holter arrhythmias†	11 (27) ($n = 41$)	2 (20) ($n = 10$)	9 (29) ($n = 31$)
Right ventricle, dimension (cm)*	2·1(0·1) ($n = 39$)	1·9(0·2) ($n = 11$)	2·2(0·1) ($n = 28$)
Structural abnormalities of tricuspid valve†	34 (65)	0 (0)	34(85)
Abnormal regurgitation†	34 (65)	0 (0)	34(85)
Systolic gradient (mmHg)*	—	—	27(2)
Pulmonary valve regurgitation†	10 (19)	1 (8)	9 (23)
TSA + TR index*	2·4(0·2)	0·5(0·1)	2·9(0·2)
Atrial contraction/early peak filling*	1·06(0·05)	1·21(0·10)§	1·01(0·05)§
Left ventricular ejection fraction*	70(1)	75(3)§	68(2)§

*Values are mean(s.e.m.); †values in parentheses are percentages. NYHA, New York Heart Association; 5-HIAA, 5-hydroxyindole acetic acid; ECG, electrocardiogram; TSA + TR, tricuspid structural abnormalities + regurgitation. ‡$P \leqslant 0·05$ (Fisher's exact test), §$P \leqslant 0·05$ (analysis of variance)

Survival analysis

Forty of 64 patients died during follow-up. Twenty-four patients died from progressive tumour disease, nine from cardiovascular disease (five cardiac deaths) and seven from unrelated diseases. The patient who had valvular replacement died from cardiovascular disease after 2 years (deficient anticoagulant therapy). Despite the high prevalence of severe tricuspid valvular disease, only one patient died from right ventricular heart failure. Survival was analysed in patients without significant tricuspid disease (TSA + TR below 1) and in patients with increasing severity of disease (*Fig. 2a*). When the TSA + TR score was 4 or greater, there was a marked effect on long-term survival, with a 5-year survival rate of 30 per cent compared with 75 per cent in patients with a normal score (TSA + TR less than 1). There were no significant differences in survival between patients with normal valves and patients with slight or moderate valvular disease. Patients with 5-HIAA excretion in excess of 500 µmol per 24 h had significantly shorter survival than those who excreted less than 500 µmol per 24 h ($P < 0·05$) (*Fig. 2b*).

The influence of eight variables on survival was investigated by univariate analysis (*Table 3*). Only older age at diagnosis, raised TSA + TR, and TR alone were shown significantly to increase the relative risk of death. Increased 5-HIAA excretion did not reach statistical significance ($P = 0·056$) with a risk ratio of 1·39 (95 per cent confidence interval 0·99–1·95). In the stepwise regression test only older age at diagnosis ($P = 0·021$) and TR ($P < 0·001$) were shown to be independent risk factors for death (*Table 3*). The risk ratio for each grade (0–4) of TR was 2·55, which indicates a more than tenfold increased risk of death for patients with TR grade 4 compared with those who have TR grade 0.

Discussion

In this series of patients with midgut carcinoid syndrome a high incidence of tricuspid abnormalities was seen at referral. The diagnosis of carcinoid heart disease requires two-dimensional echocardiographic and Doppler examinations to assess the severity of valvular stenosis and regurgitation. In general, ECG and chest

Table 2 Clinical and cardiological characteristics related to the severity of tricuspid abnormalities

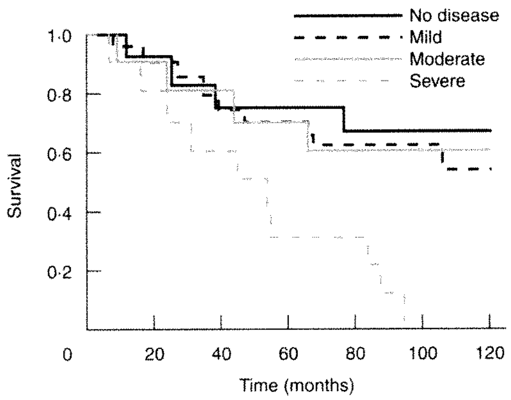
	TSA + TR index			
	< 1 (*n* = 12)	1–2·5 (*n* = 20)	3–3·5 (*n* = 10)	≥ 4 (*n* = 10)
Clinical				
Age at diagnosis (years)*	63(3)	62(2)	56(4)	61(3)
Sex ratio (F : M)	9 : 3	11 : 9	5 : 5	6 : 4
Functional class (NYHA)*	1·5(0·2)	1·4(0·2)	1·5(0·2)	1·0(0·0)
Systolic blood pressure (mmHg)*	154(6)	143(5)	138(9)	132(8)
Hypertension	7	3	1	2
Urinary 5-HIAA at referral (μmol per 24 h)*	306(105)	556(163)	408(86)	901(196)
Pathological chest radiography findings	0	1	3	2
Forced expiratory volume in 1 s (litres)*	2·8(0·4)	3·0(0·3)	3·0(0·3)	2·9(0·3)
Follow-up (months)*	107(22)	91(11)	120(29)	50(10)
Deaths	6†	10†	6†	10†
From cardiovascular disease	3	1	1	3
From heart disease	2	1	1	1
Palliatively treated, alive	3	5	3	0
Cardiological				
Ischaemic heart disease	2	4	1	1
Pathological ECG at rest	7	6	4	6
Holter arrhythmias	2(20) (*n* = 10)	5(29) (*n* = 17)	1(11) (*n* = 9)	3(60) (*n* = 5)
Right ventricle, dimension (cm)*	1·9(0·2) (*n* = 11)	2·2(0·1) (*n* = 17)	2·4(0·2) (*n* = 7)	2·0(0·2) (*n* = 4)
Structural abnormalities of tricuspid valve	0	14	10	10
Abnormal regurgitation	0	15	9	10
Systolic gradient (mmHg)*	—	25(2)	26(3)	29(3)
Pulmonary valve regurgitation	1	2	3	4
Atrial contraction/early peak filling*	1·21(0·10)‡	0·96(0·10)‡	1·06(0·05)‡	1·10(0·10)‡
Left ventricular ejection fraction*	75(3)	68(2)	68(3)	69(4)

*Values are mean(s.e.m.). NYHA, New York Heart Association; 5-HIAA, 5-hydroxyindole acetic acid; ECG, electrocardiogram; TSA + TR, tricuspid structural abnormalities + regurgitation. †$P < 0·05$ (Fisher's exact test), ‡$P < 0·001$ (analysis of variance)

radiography are non-specific in the early course of the disease.

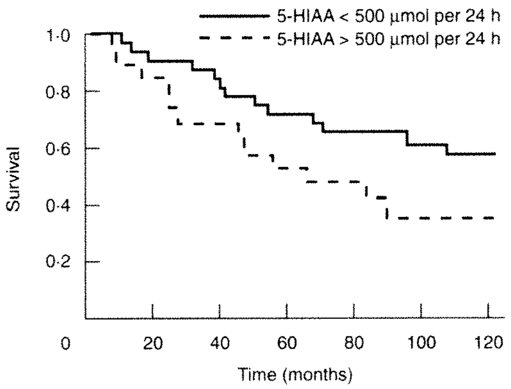
The combination of superficial and right ventricular cardiac lesions suggests a bloodborne tumour product, released from liver metastases, as a causative agent. 5-HT, with its potent fibroblast-proliferative action, was one of the first candidate agents proposed. Waldenström and Ljungberg[14] suggested an interaction between 5-HT, platelets and the endothelium leading to changed permeability and valvulitis. The 5-HT hypothesis also has support from the high incidence of myocardial fibrosis associated with diets rich in 5-HT[15] and from the observation of fibroblast proliferation of retroperitoneum and endocardium after administration of certain drugs with 5-HT receptor activity, e.g. ergot alkaloids[9]. Appetite-suppressant drugs such as fenfluramine[16,17], which release 5-HT and inhibit its reuptake[18], have been shown to induce valvular deformities. In a guinea-pig model pronounced endocardial proliferation was elicited by a combination of 5-HT excess, impaired liver function and tryptophan deficiency, a situation mimicking the carcinoid syndrome[19].

In some studies no relation between the severity of cardiac disease, extent or duration of tumour disease was seen[20]. Since carcinoid tumours may produce several fibroblast-proliferative agents besides 5-HT, e.g. tachykinins and transforming growth factor β, the pathogenetic 5-HT mechanism has been questioned[21–23]. In the present series patients with excessive urinary excretion of 5-HIAA had a reduced survival on Kaplan–Meier analysis but 5-HIAA levels were not shown to be an independent risk factor in multivariate analysis, in contrast to increased age or severe TR. Even though the majority of deaths observed were due to tumour progression, severe TR was strongly correlated with poor survival indicating that the valves are targets reflecting several aspects of the tumour disease, i.e. duration, tumour burden and secretory activity. In a recent study of 23 patients with the carcinoid syndrome[24] only post-treatment 5-HIAA levels independently predicted the development of valvular heart disease. Some early series failed to show an impact of 5-HIAA levels[20,25], but in more recent studies raised 5-HIAA levels were clearly related to cardiac disease[6,7]. Himelman and Schiller[26] found a four-



No. at risk							
No disease	12	11	9	9	8	6	3
Mild disease	20	18	15	14	10	9	7
Moderate disease	10	9	8	7	6	5	4
Severe disease	10	8	6	3	3	0	0
Total	52	46	38	33	27	20	14

a Disease severity



No. at risk							
Low 5-HIAA	31	28	24	22	20	17	11
High 5-HIAA	19	16	13	10	7	3	3
Total	50	44	37	32	27	20	14

b 5-HIAA level

Fig. 2 **a** Survival after diagnosis of patients with or without tricuspid valvular changes, according to disease severity. **b** Survival of patients according to urinary 5-hydroxyindole acetic acid (5-HIAA) level at referral (above or below 500 µmol per 24 h)

Table 3 Univariate analysis of death risk and stepwise identification of predictors of death in 52 patients with carcinoid

	P	Risk ratio
Univariate analysis		
Tricuspid abnormalities*	0·002	1·41 (1·13–1·76)
Tricuspid regurgitation	< 0·001	2·52 (1·59–3·99)
Tricuspid structural abnormalities	0·121	1·30 (0·93–1·83)
Age	0·004	1·06 (1·02–1·11)
Female sex	0·871	1·06 (0·52–2·18)
Urinary 5-HIAA	0·056	1·39 (0·99–1·95)
Systolic blood pressure	0·234	0·99 (0·97–1·01)
Ejection fraction	0·923	1·00 (0·96–1·04)
Stepwise identification of predictors		
Tricuspid regurgitation	< 0·001	2·55 (1·56–4·18)
Age	0·021	1·06 (1·01–1·11)

Values in parentheses are 95 per cent confidence intervals. *Tricuspid structural abnormalities + regurgitation; 5-HIAA, 5-hydroxyindole acetic acid

fold increase in patients with cardiac disease and proposed a threshold effect of the 5-HT load (5-HIAA levels exceeding 400 µmol per 24 h) for development of valvular heart disease. A strong correlation between high circulating 5-HT levels and carcinoid heart disease has been demonstrated in 19 patients by cardiac catheterization and echocardiography, suggesting a major role of 5-HT in the pathogenesis of heart disease[27]. The high sensitivity and low specificity of raised serum 5-HT levels as a marker for cardiac disease suggest that 5-HT is a necessary, but not the only responsible, agent. Additive factors could be the duration of 5-HT load, genetic disposition or cosecreted humoral agents.

Interventional and medical treatment of patients with the carcinoid syndrome aims to reduce disabling hormonal symptoms, but also to retard development of carcinoid cardiac disease. Patients who underwent curative liver resection or had ischaemic treatment of bilobar liver disease had prolonged reduction of 5-HIAA excretion[11] with a 5-year survival rate of 69 per cent when tumour-related deaths were studied and ten medically treated patients with poor prognosis included, but an overall 5-year survival rate of 58 per cent. Patients with a high TSA + TR score (4 or more) at referral had markedly reduced long-term survival, usually due to tumour progression and seldom to cardiac disease. This may reflect a beneficial effect of active tumour treatment on progressive carcinoid heart disease in the present series. Two reports have previously indicated a survival disadvantage of valvular disease in the carcinoid syndrome. Himelman and Schiller[26] reported that the survival after echocardiography at referral was shorter for patients with cardiac disease than for those without (1·9 *versus* 3·8 years). In the large series by Pellikka *et al.*[7] the 5-year survival rate for patients with cardiac involvement was similarly low (20 *versus* 50 per cent). In the present series the corresponding figures were 30 *versus* 75 per cent. Robiolio *et al.*[27] found no survival differences between patients with or without carcinoid heart disease.

Although separately developed and using one additional grade for scoring (0 for normal), the scoring system in this study for valvular abnormalities and regurgitation is similar to that described by Denney *et al.*[24]. The relative absence of pulmonary stenosis in the present study might be due to inadequate visualization of the pulmonary valves. Pellikka *et al.*[7] reported pulmonary stenosis in about half of their patients, in whom Doppler examination was also performed, and pulmonary regurgitation in 80 per cent.

The indications and proper timing of valve replacement in these seriously ill patients have been debated. Bioprostheses might offer an advantage with a minor risk of thrombosis even though progressive deterioration of new valves has been reported[28]. In a study from the Mayo Clinic 26 patients with symptomatic carcinoid heart disease received valvular replacement (20 mechanical and six bioprosthetic) for severe tricuspid regurgitation[29]. During the perioperative period, one-third died from postoperative bleeding and right heart failure. On the other hand, the survivors had substantially improved function and long-term survival. The prognosis after valve replacement was particularly favourable for patients with a relatively low level of 5-HIAA excretion. In a recent review, the mortality rate within 30 days of valvular surgery was 56 per cent for elderly patients (above 60 years) *versus* zero for younger patients[30]. Considering the high mean age of patients with midgut carcinoid syndrome in most series, a careful selection of patients for valve replacement is necessary. A close collaboration with expert cardiologists may reduce, or retard, the need for valve replacement. Active treatment of the tumour disease can give long-term reduction of tumour secretion, but its influence on progressive valvular disease is largely unknown. In individual patients with relatively stable tumour disease rapid progression of valvular deformities has been observed[31], which necessitates echocardiography and clinical observation at regular intervals for all patients with the carcinoid syndrome.

Acknowledgements

The authors acknowledge the technical assistance of the staff at the Department of Clinical Physiology, Sahlgrenska University Hospital, and the statistical calculations made by Thomas Karlsson, Institute of Heart and Lung Diseases, Gothenburg University, Gothenburg, Sweden. The study was supported by grants from the Swedish Heart and Lung Foundation, the Swedish Medical Research Council (5220) and the IB & A Lundberg Research Foundation.

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Original article

Risk factors for complications following resection of large gastric cancer

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Background: Although there is a low mortality rate after gastrectomy in Japan, most studies include many early gastric cancers. There have been few studies on the morbidity after gastrectomy for advanced gastric cancer. The aim of this study was to clarify the characteristics and risk factors for postoperative complications after resection of large gastric cancers based on three clinical factors: patient, operation and tumour.

Methods: A retrospective study was carried out on 97 patients with a gastric tumour measuring 10 cm or more in diameter. Postoperative complications were recorded and the patients were divided into two groups: 38 with complications and 59 without. Patient, operative and tumour findings were compared between the two groups.

Results: Overall morbidity and mortality rates were 39 and 7 per cent respectively. The most frequent complication was pleural effusion (17 per cent), followed by anastomotic leakage (14 per cent), abdominal abscess (12 per cent), wound infection (12 per cent), pancreatic leakage (8 per cent) and peritonitis (6 per cent). Risk factors associated with postoperative complications were operating time (400 *versus* 337 min, $P < 0.01$), blood loss (1338 *versus* 782 ml, $P < 0.01$), pancreatic invasion (26 *versus* 8 per cent, $P < 0.05$) and raised serum carcinoembryonic antigen (CEA) level (5 ng/ml or greater) (36 *versus* 17 per cent, $P < 0.05$), independent of patient age, nutritional status, type of gastrectomy, splenectomy or pancreatectomy, extent of lymph node dissection, tumour location, size and stage of disease.

Conclusion: Even in Japan, the morbidity of gastrectomy for large gastric cancer is high and associated with operating time, blood loss, pancreatic invasion and serum CEA level.

Paper accepted 5 February 2001

British Journal of Surgery 2001, 88, 873–877

Introduction

Controversy still surrounds the issue of whether aggressive operative treatment improves the survival of patients with gastric cancer[1–4]. Gastric surgeons in Japan have performed radical gastrectomy and extended lymph node dissection with mortality rates of less than 1 per cent[5,6]. However, several clinical trials in Europe have shown high morbidity and mortality rates with no survival benefit after radical surgery for gastric cancer[7–9]. The difference in morbidity and mortality between Japanese and Western countries is thought to be due to patient age, the presence or absence of cardiopulmonary disease, different physical characteristics, and differences in the management of complications[8,9].

Splenectomy and distal pancreatectomy associated with extended lymph node dissection (D_2, D_3) are the factors that have most effect on morbidity and mortality following gastrectomy for cancer[10–12]. Although low morbidity and mortality rates after radical gastrectomy have been reported by a number of Japanese authors[6,13], these studies include many fit patients with early stage tumours. There have been few comprehensive studies on morbidity and mortality after gastrectomy for advanced gastric cancer in Japan, and the characteristics and risk factors for postoperative complications are still unclear[14].

Recently, the authors examined morbidity after D_2 and D_3 gastrectomy in patients with node-positive gastric cancer and clarified that postoperative complications occurred frequently (36 per cent) and were associated with total gastrectomy, splenectomy, long operating time and blood transfusion[15]. In the present study, large gastric cancer was defined as a tumour measuring 10 cm or more in diameter[16], and characteristics and risk factors for complications after resection of large gastric cancer were investigated for three groups of clinical factors, namely those related to the patient, the operation and the tumour.

Patients and methods

A retrospective study was carried out on a consecutive series of 97 patients with histologically diagnosed adenocarcinoma of the stomach measuring 10 cm or more in size. All patients underwent primary gastrectomy.

The patients' age and sex, symptoms, type of gastrectomy, presence or absence of splenic or pancreatic resection, extent of lymph node dissection, operating time, blood loss and transfusion requirements were obtained from the operative records and medical notes. Details of the location, size, gross type and histological type of the tumour, depth of wall invasion, level of lymph node metastasis, pancreatic invasion, liver metastasis, peritoneal dissemination, stage of disease and operative curability were obtained from the pathology reports. These findings were assessed according to the Japanese classification of gastric carcinoma outlined by the Japanese Gastric Cancer Association[17].

Preoperative blood results were obtained from the notes. These included haemoglobin level, lymphocyte count, total protein, albumin and cholesterol levels, carcinoembryonic antigen (CEA) level and C-reactive protein (CRP) concentration. The prognostic nutritional index (PNI) was calculated as: PNI = (albumin level × 10) + (lymphocyte count × 0·005).

Postoperative complications were recorded. Anastomotic leakage and abdominal abscess were confirmed by radiological examination, and pancreatic leakage was diagnosed by a high concentration of amylase in the discharge. Operative death was defined as a hospital death within 30 days of operation, and mortality included all hospital deaths.

Differences were analysed with the χ^2 test for categoric variables and the t test for continuous variables. $P < 0{\cdot}05$ was considered statistically significant.

Results

This patient group consisted of 42 patients with stage IV tumour, 40 with stage III, nine with stage II and six with stage I. Most patients (95 per cent) had tumours involving the subserosa, serosa or adjacent organs. There were seven hospital deaths including two operative deaths (2 per cent). Six patients died from sepsis or multiple organ failure following anastomotic leakage, abdominal abscess and peritonitis. Four of the six patients underwent reoperation including abdominal lavage and drainage. The overall morbidity and mortality rates were 39 per cent (38 patients) and 7 per cent respectively; and 11 reoperations were performed in eight patients (8 per cent).

The most frequent complication was pleural effusion (17 per cent), followed by anastomotic leakage (14 per cent), abdominal abscess (12 per cent), wound infection (12 per cent), pancreatic leakage (8 per cent) and peritonitis (6 per cent). Perforation of the transverse colon in two patients was associated with ischaemic necrosis after extended resection of the mesocolon. Liver failure in two patients occurred after anastomotic leakage and abdominal abscess, peritonitis or sepsis. Some complications needed reoperation: four of 14 patients with anastomotic leakage, two of 12 with abdominal abscess or peritonitis, one of three with intestinal perforation, and one of one with intestinal obstruction.

There was no significant difference between patients with and without complications with respect to age (62·7 *versus* 62·9 years), male sex (66 *versus* 59 per cent), epigastric pain (34 *versus* 41 per cent), haemoglobin level (10·8 *versus* 11·1 g/dl), lymphocyte count (1640 *versus* 1496 per mm^3), total protein concentration (5·7 *versus* 5·9 g/dl), albumin level (3·4 *versus* 3·5 g/dl), cholesterol concentration (152 *versus* 160 mg/dl), PNI (41·9 *versus* 42·4) and raised CRP level (52 *versus* 41 per cent).

Table 1 shows the operative data. Operating time was significantly longer and blood loss significantly greater in patients with complications than in those without. In both groups, most patients received blood transfusions and the frequency of total gastrectomy, extended lymph node dissection (D_3) and operation performed in the 1980s was not significantly different.

When tumour data were examined, pancreatic invasion (26 *versus* 8 per cent, $P < 0{\cdot}05$) and serum CEA level of 5 ng/ml or greater (36 *versus* 17 per cent, $P < 0{\cdot}05$) were observed more often in patients with complications than in those without. However, there was no significant difference between patients with complications and those without with regard to tumour location (upper third), size, Borrmann type, histological differentiation, T_3 invasion, extended lymph node metastasis (n2, n3), the presence of liver metastasis, peritoneal dissemination, stage IV disease and non-curative resection.

Discussion

In this study, morbidity and mortality rates after gastrectomy for large gastric cancer were high (39 and 7 per cent respectively), and common complications were pleural effusion, anastomotic leakage, abdominal abscess, wound infection and pancreatic leakage. Although most complications were managed successfully without operation, some patients (8 per cent) needed reoperation. Previous studies have indicated that these complications are characteristic

Table 1 Operative factors

	Complications ($n = 38$)	No complications ($n = 59$)
Gastrectomy		
Total	31 (82)	41 (69)
Distal	7 (18)	18 (31)
Combined resection of spleen or pancreas		
Yes	23 (61)	30 (51)
No	15 (39)	29 (49)
Lymph node dissection		
D_3	16 (42)	21 (36)
D_1, D_2	22 (58)	38 (64)
Operating time (min)		
Mean(s.d.)	400(99)	337(85)*
≥ 360	29 (76)	22 (37)
< 360	9 (24)	37 (63)†
Blood loss (ml)		
Mean(s.d.)	1338(1164)	782(494)*
≥ 800	24 (63)	21 (36)
< 800	14 (37)	38 (64)†
Blood transfusion		
Yes	32 (84)	51 (86)
No	6 (16)	8 (14)
Decade of operation		
1980s	20 (53)	31 (53)
1990s	18 (47)	28 (47)

Values in parentheses are percentages unless otherwise indicated. $^*P < 0.01$ *versus* complications (t test); $†P < 0.01$ *versus* complications (χ^2 test)

for patients undergoing total gastrectomy with splenectomy and pancreatectomy[14,15,18,19]. These procedures require opening and removal of the pancreatic capsule, and damage the parenchyma and small ducts of the pancreas[20]. As six of seven hospital deaths in the present series were directly associated with anastomotic leakage complicating abdominal abscess or peritonitis, early diagnosis and proper management is essential when anastomotic leakage is suspected.

There are few comprehensive studies evaluating the risk factors for complications after gastrectomy for cancer[14,15]. This study divided the clinical parameters into patient-, operation- and tumour-related factors, and identified that factors associated with the presence or absence of post-operative complications were the duration of operation, volume of blood loss, presence of pancreatic invasion and raised serum CEA level. Previous studies have also indicated that duration of operation and volume of blood loss are associated with the morbidity after gastrectomy[15]. Volume of blood transfusion may adversely affect the survival of patients after gastrectomy for cancer[7,21]; therefore, blood loss and transfusion should be minimized by careful operative technique.

Recent reports demonstrate that morbidity and mortality after gastrectomy vary between authors, countries and procedures[22–24]. Morbidity rates range from 13 to 46 per cent after D_2 gastrectomy and from 19 to 50 per cent after D_3 gastrectomy, whereas mortality rates range from 0 to 13 per cent after D_2 gastrectomy and from 0 to 7 per cent after D_3 gastrectomy[7–9,12,15,22–29]. Patient characteristics and definitions of morbidity and mortality vary between reports. The present study included only patients with large gastric cancers measuring 10 cm or more; postoperative complications included every trivial event; and mortality was expressed as all hospital deaths. Accordingly the morbidity and mortality rates were rather high (39 and 7 per cent respectively), and the incidence of postoperative complications was not different between D_2 and D_3 dissections (37 *versus* 43 per cent). The high morbidity rate found in this series is in accordance with a previous Japanese study on patients with node-positive gastric cancer[15], and there was no hospital death in the most recent 10 years.

English language reports (including Japanese series) of morbidity and mortality after gastrectomy with or without splenectomy[6,10,15,18,30–32] indicate that the morbidity after gastrectomy with splenectomy is much higher than that after gastrectomy alone. Many reports have shown that splenectomy is linked to an increased morbidity rate, and there is no evidence that splenectomy improves survival[18,19,32,33]. Splenectomy should not be performed unless the tumour directly invades the spleen or involves the splenic hilar lymph nodes. D_2 dissection without splenectomy is recommended as a standard operation for advanced gastric cancer[34].

It was noteworthy that the age and nutritional status of patients did not influence the frequency of complications in this study. Several studies have suggested that anaemia, hypoproteinaemia and hypoalbuminaemia are associated with higher postoperative morbidity and mortality rates, and that serum albumin concentration is an independent parameter for adverse surgical outcome[35,36]. The present data suggest that operative factors influence the frequency of postoperative complications more strongly than patient factors when patients with large gastric cancers are treated by radical gastrectomy.

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Original article

Endotoxin, cytokines and lipid peroxides in children with intussusception

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Background: Intussusception is a relatively common paediatric surgical emergency. The aim of this study was to investigate selected inflammatory mediators in children with acute intussusception and to identify potentially useful plasma markers of clinical outcome.

Methods: Clinical, radiographic, operative and pathological details were recorded prospectively of all children presenting to a single institution with a confirmed diagnosis of acute intussusception during 1 year. Paired acute and convalescent venous blood samples were collected in a standard manner for blinded analysis of the following: malondialdehyde, C-reactive protein (CRP), interleukin (IL) 6, neopterin, tumour necrosis factor α, endotoxin, and immunoglobulin (Ig) G and IgM antiendotoxin core antibody (EndoCAb).

Results: Thirty-two consecutive children (23 boys, nine girls) with a median age of 4 months were studied. Acute ileocolic intussusception was managed by air enema reduction ($n = 19$), operative reduction ($n = 8$) or surgical resection ($n = 5$). Peripheral blood cultures were sterile. Acute levels of plasma IL-6, neopterin and CRP were significantly raised in comparison to both normal laboratory ranges and convalescent samples ($P < 0.001$). Using stepwise discriminant analysis, CRP was identified as the best variable at distinguishing between the three treatment groups ($P < 0.001$). IgM EndoCAb concentrations were significantly greater in the convalescent sera of all the patients ($P < 0.001$).

Conclusion: Acute ileocolic intussusception in childhood is associated with endotoxinaemia and significantly raised levels of circulating inflammatory cytokines. Plasma CRP at diagnosis showed a statistically significant positive correlation with disease severity.

Preliminary data presented to the American Paediatric Surgical Association 30th Annual Meeting, Rancho Mirage, California, USA, May 1999

Paper accepted 16 February 2001

British Journal of Surgery 2001, 88, 878–883

Introduction

Intussusception is one of the commonest abdominal emergencies in childhood. The incidence of the condition in Western societies is approximately 2·3 per 1000 live births and almost two-thirds of cases occur in infancy[1,2]. Untreated acute ileocolic intussusception usually progresses to intestinal strangulation, perforation, sepsis and fatal multiple organ failure. Even with appropriate treatment, some children with apparently uncomplicated intussusception become severely ill and develop multiple organ failure[3]. The key inflammatory mediators involved in acute intussusception have not been studied systematically. In this study, plasma cytokines (interleukin (IL) 6 and tumour necrosis factor (TNF) α), free radicals (lipid peroxides) and endotoxin were investigated in children with intussusception, with the aim of achieving a better understanding of the disease process and in an attempt to identify potentially useful markers of disease outcome.

Patients and methods

The parents of all children presenting to a single institution during 1 year (1997–1998) with a confirmed diagnosis of intussusception were invited to participate in the study;

The Editors have satisfied themselves that all authors have contributed significantly to this publication

written informed parental consent was obtained in each case. Clinical, radiographic, operative and pathological details were recorded for each patient. In addition to routine haematological investigations, a further 5 ml of peripheral venous blood was collected in a standard manner for subsequent analysis ('acute sample'). A second blood sample was obtained from each child after full recovery before discharge home and processed in an identical manner ('convalescent sample'). Stool, midstream urine and peripheral blood cultures were also obtained from each patient.

For the endotoxin assays, free-flowing blood samples were collected into tubes without additive using a no-touch technique, centrifuged at 626*g* for 10 min, and the serum stored at –75°C. For cytokine, malondialdehyde (MDA) and C-reactive protein (CRP) estimations, free-flowing venous blood was collected into ethylenediamine tetra-acetic acid Vacutainer™ tubes (Becton, Dickinson and Company, Plymouth, UK), centrifuged at 626*g* for 10 min, and the plasma was stored in aliquots at –75°C. Haemolysed samples were discarded.

Assays were performed for MDA, CRP, IL-6, neopterin, TNF-α, endotoxin, immunoglobulin (Ig) G antiendotoxin core antibody (IgG EndoCAb) and IgM antiendotoxin core antibody (IgM EndoCAb) by independent investigators blinded to the clinical details of individual patients. Each laboratory was subject to strict quality control and all assays were undertaken using validated methods. Interassay and intra-assay coefficients of variation were below 10 per cent.

This study was carried out after obtaining institutional ethics committee approval and in accordance with institutional ethical guidelines.

Cytokine assays

Plasma samples were assayed for circulating TNF-α, IL-6 and neopterin in duplicate using commercially available enzyme-linked immunosorbent assays (EASIA assays; Medgenix Diagnostics, Fleurus, Belgium).

Malondialdehyde assay

MDA, a marker of lipid peroxidation, was assayed by high-performance liquid chromatography (HPLC) as described previously[4]. Boiling serum in acid solution containing thiobarbituric acid achieved simultaneous hydrolysis of lipid peroxide and reaction of the generated MDA. Excess production of MDA from non-lipid peroxide sources was inhibited by the addition of butylated hydroxytoluene. The reaction was stopped by immersing the tubes in iced water. The coloured product was then extracted with butanol/ethyl acetate, evaporated to dryness, redissolved in the HPLC mobile phase and injected on to the HPLC column, where it was separated by reverse-phase HPLC and measured at 532 nm.

C-reactive protein assay

Plasma levels of CRP were assayed in duplicate by an immunoturbidimetric method using commercially available kits according to the manufacturer's recommendations (Tina-quant CRP; Roche, Welwyn Garden City, UK). The normal plasma CRP concentration in children is below 5 mg/l.

Endotoxin assay

Endotoxin was measured by the Chromogenix colorimetric kinetic limulus amebocyte lysate kit method (Chromogenix, New York, USA). Samples were diluted 1 : 10 in pyrogen-free water and heat treated at 85°C for 10 min. The kit endotoxin standard was diluted in 1 : 10 normal serum in pyrogen-free water (heat treated) and made up in a series of 12 doubling dilutions from 24 endotoxin units (EU)/ml for the quantitative standard curve. Time to onset of the reaction was measured at 405 nm optical density in a Thermomax reader (Molecular Devices, Woking, UK) and results determined in EU from the standard curve using SoftMax software (Molecular Devices)[5].

Endogenous antiendotoxin core antibody assays

EndoCAbs were measured by methods described previously[5,6]. In brief, microplates were coated with equimolar amounts of polymyxin complexes of an Rc or Rd lipopolysaccharide from each of four Gram-negative species and blocked with bovine serum albumin. Dilutions of test sera (1 : 200) were added in triplicate, and eight doubling dilutions of a calibrated pooled serum standard with a high IgG EndoCAb titre were run on each plate as a quantitative standard curve. After incubation and washing, plates were developed with γ-chain-specific (IgG) or μ-chain specific (IgM) alkaline phosphatase conjugates (Zymed, San Francisco, California, USA), followed by para-nitro phenylphosphate alkaline phosphatase substrate (Sigma-Fast; Sigma, Poole, UK). Optical densities at 405 nm were read on an automated plate reader (Molecular Devices) with SoftMax software. Results were determined in median units (100 median units = median of healthy adult IgG or IgM EndoCAb normal range).

Statistical analysis

Statistical comparisons between acute and convalescent values were made by using the Wilcoxon signed rank test for paired non-parametric data. Comparison between subgroups (non-operative; surgery, no resection; surgery and resection) was by the Kruskal–Wallis test. The data were normalized by natural logarithmic transformation primarily to enable discriminant analysis, which was used to determine which variable was best at distinguishing between the three subgroups. Statistical significance was accepted at $P < 0{\cdot}05$. SPSS for Windows (Version 8; SPSS, Chicago, Illinois, USA) was used for the analysis.

Results

Clinical features

Of 35 consecutive children with acute intussusception, 32 (23 boys and nine girls) with a median age of 4 (range 2–19) months were recruited. Parents of two children declined to enrol their child in the study, and one child with a postoperative small bowel intussusception was not included. Symptoms and signs of intussusception were present for a median of 2 (range 1–8) days before referral and most commonly comprised abdominal pain (n = 30), bilious vomiting (n = 26), bloody stools (n = 24) and a palpable abdominal mass (n = 20). Duration of symptoms was not significantly longer in infants who needed intestinal resection. Three children had experienced a recent symptomatic upper respiratory tract infection or gastroenteritis.

After initial assessment (including blood tests) and resuscitation with 4·5 per cent human albumin solution (median volume 20 (range 10–140) ml/kg), an ileocolic intussusception was confirmed in all children by abdominal ultrasonography. In each case, prophylactic intravenous broad-spectrum antibiotics and morphine analgesia were administered followed by an attempt at air enema reduction. A successful non-operative reduction was achieved in 19 children (19 of 27 reducible intussusceptions) using a median sustained pressure of 100 (range 60–120) mmHg. Thirteen children required laparotomy; five needed intestinal resection for an irreducible intussusceptum. No intussusception had reduced spontaneously before laparotomy. Histological examination of resected specimens confirmed the presence of non-viable bowel with lymphoid hyperplasia in four and a gangrenous Meckel's diverticulum in one patient. There were no deaths. All recovered uneventfully, except one girl who required four laparotomies, an extensive small bowel resection, parenteral nutrition and a temporary ileostomy. She subsequently made a full recovery.

Laboratory data

All peripheral blood cultures were sterile but two children had a concomitant urinary tract infection (enterococcus, coliform) and two had pathogens isolated from stool cultures (*Campylobacter* sp. and rotavirus). Routine haematological and biochemical results were within normal limits on admission, except for mild hypoalbuminaemia in six patients and a raised peripheral white blood cell count in three children.

Acute levels of plasma IL-6 and neopterin were significantly raised in comparison to both normal laboratory ranges and levels in convalescent samples (*Table 1*). TNF-α concentrations were raised in both acute and convalescent samples but there was no significant overall difference between these two samples. Statistically significant differences between acute samples in the operative and

Table 1 Plasma values in 32 children with acute ileocolic intussusception

	Non-operative (n = 19)	Operative reduction (n = 8)	Intestinal resection (n = 5)	All children (n = 32)
IL-6 (pg/ml)				
Acute	16·9 (10·2–29·9)	24·0 (14·4–37·6)	17·2 (9·3–4244)	18·8 (10·6–30·4)
Convalescent	2·0 (2·0–5·7)	9·3 (3·2–58·3)	3·5 (2·4–281)	3·0 (2·0–9·2)*
MDA (μmol/l)				
Acute	2·66 (2·26–3·00)	2·77 (2·44–3·10)	1·84 (1·78–2·32)	2·59 (2·18–2·92)
Convalescent	2·80 (2·54–3·32)	3·07 (2·37–3·58)	2·50 (2·20–3·12)	2·86 (2·39–3·33)
TNF-α (pg/ml)				
Acute	28·1 (19·6–36·6)	44·1 (30·7–64·7)	30·9 (29·6–63·7)	30·6 (24·7–38·5)
Convalescent	37·3 (16·3–47·6)	57·4 (30·6–64·8)	32·8 (25·2–47·1)	39·8 (20·5–50·5)
Neopterin (ng/ml)				
Acute	1·62 (1·17–1·82)	2·82 (2·49–3·16)	2·74 (2·07–3·13)	1·88 (1·62–2·73)
Convalescent	1·09 (0·39–1·50)	1·42 (1·06–2·16)	1·53 (1·42–1·83)	1·20 (1·04–1·68)*

Values are median (interquartile range). IL, interleukin; MDA, malondialdehyde; TNF, tissue necrosis factor. Normal adult reference ranges: IL-6 < 8·5 pg/ml; MDA 2·4–6·1 μmol/l; TNF-α < 20 pg/ml; neopterin < 2·48 ng/ml. *$P < 0{\cdot}001$ *versus* acute (Wilcoxon signed rank test)

Table 2 Plasma C-reactive protein concentrations in 32 children with acute ileocolic intussusception

	Plasma C-reactive protein (mg/l)			
	Non-operative reduction ($n = 19$)	Operative reduction ($n = 8$)	Intestinal resection ($n = 5$)	All children ($n = 32$)
Acute	36·1 (28·9–38·4)	54·6 (48·3–57·9)	129·7 (119·4–136·2)	38·9 (35·2–57·0)
Convalescent	8·3 (3·9–9·0)*	9·1 (5·4–9·9)*	15·2 (10·7–17·0)*	8·8 (4·8–9·7)*

Values are median (interquartile range). $^*P < 0{\cdot}001$ *versus* acute (Wilcoxon signed rank test). $P < 0{\cdot}001$ between subgroups for acute samples (Kruskal–Wallis test)

Table 3 Endotoxin and antiendotoxin core antibody levels in acute and convalescent samples from 32 children with acute intussusception

	Non-operative reduction ($n = 19$)	Operative reduction ($n = 8$)	Intestinal resection ($n = 5$)	All children ($n = 32$)
Endotoxin (EU/ml)				
Acute	0·01 (0–0·03)	0·02 (0·01–0·08)	0·03 (0·02–0·44)	0·01 (0·01–0·04)
Convalescent	0·01 (0–0·10)	0·01 (0–0·11)	0·04 (0–0·22)	0·01 (0–0·09)
IgM EndoCAb (MMU/ml)				
Acute	37·0 (15·6–73·6)	39·2 (26·2–73·5)	31·6 (27·7–195·7)	37·6 (24·8–74·6)
Convalescent	178·1 (78·8–327·3)	157·5 (22·2–205·8)	289·2 (149·9–300·8)	180·4 (63·4–290·9)*
IgG EndoCAb (GMU/ml)				
Acute	38·6 (19·8–60·6)	19·0 (10·3–66·3)	50·0 (21·0–79·1)	31·4 (15·9–56·3)
Convalescent	26·7 (22·6–64·8)	22·3 (5·9–47·8)	61·8 (47·2–84·1)	32·6 (22·2–62·1)

Values are median (interquartile range). Ig, immunoglobulin; EndoCAb, antiendotoxin core antibody. $^*P < 0{\cdot}001$ *versus* acute (Wilcoxon signed rank test)

non-operative groups were observed for neopterin ($P = 0{\cdot}001$) (*Table 1*). MDA concentrations were not significantly different in acute and convalescent samples and in patients undergoing intestinal resection. Plasma CRP concentrations were significantly raised in acute samples, both in comparison to levels in convalescent samples and to the normal laboratory reference range (less than 5 mg/l) (*Table 2*). Statistically significant differences between the acute samples were observed for plasma CRP on subgroup analysis; the CRP concentration was greatest in patients who needed intestinal resection followed by that in patients who had a laparotomy for reduction of intussusception, and least in children who had successful enema reduction (*Table 2*).

Considering all patients with intussusception, endotoxin concentrations were not significantly different between acute and convalescent samples, taken 2–6 days later in most cases (*Table 3*). However, levels of IgM EndoCAb were significantly greater in the convalescent sera of all subgroups of patients with intussusception ($P < 0{\cdot}001$).

Statistically significant differences between acute sample concentrations for the three intussusception subgroups were found for only two variables, CRP and neopterin. Using stepwise discriminant analysis, CRP was identified as the best variable at distinguishing between the three subgroups ($P < 0{\cdot}001$), with no further advantage gained from including other variables.

Discussion

The mortality rate associated with intussusception has declined steadily in developed countries and is now less than 1 per cent[3]. However, serious morbidity is not uncommon, particularly in patients with a delayed diagnosis[2]. The biological mechanisms involved in complicated intussusception are poorly understood, although intestinal ischaemia–reperfusion injury may be important in some cases. The role of free radicals, inflammatory cytokines and endotoxin has been speculative. This study was designed to explore which of these factors might be involved in the systemic aspects of the disease. This knowledge may help to provide an early indicator of disease severity and yield new insights into therapeutic strategies in severe cases.

Hydrostatic or air enema reduction is usually only possible if the intestine is viable and it is almost always unsuccessful in the presence of strangulated intestine.

Consequently, failure of enema reduction is strongly correlated with the more severe forms of intussusception. Overzealous attempts to reduce the intussusception in these severe cases is hazardous. Plasma markers might be valuable to help determine from the outset which children are more likely to have strangulated bowel so that urgent surgery can be performed.

Acute intussusception results in local inflammation and vascular congestion. Activation of leucocytes causes the release of inflammatory mediators. Inflammatory cytokines promote leucocyte adhesion and migration through post-capillary vascular endothelium, and contribute to microvascular disturbances leading to hypovolaemia and bacterial translocation through the gut wall[7]. Neopterin (D-erythro-6-(1′,2′,3′-trihydroxypropyl)pterin) is a metabolite of guanosine triphosphate and is secreted in large quantities by activated macrophages under stimulation by interferon γ[8]. Increased plasma neopterin concentrations have been found to correlate with disease severity in acute pancreatitis and with death in critically ill adult patients[9,10]. Significantly raised levels of plasma IL-6 and neopterin were detected in these children with acute intussusception, particularly in those who needed operative intervention, suggesting that plasma concentrations of these cytokines may be linked to disease severity. TNF-α concentrations, although increased, were similar in acute and convalescent samples. However, TNF-α has a short circulating half-life[11] and an early but transient release of this cytokine in acute intussusception might have been missed.

Plasma CRP concentration was significantly raised at diagnosis in acute intussusception, with a direct correlation to disease severity, and proved to be the best marker in this study. Plasma CRP is easily measured and routinely available in most laboratories. It deserves further investigation as a potentially valuable index of disease severity at the time of diagnosis of intussusception. Measurement of CRP may predict children with an irreducible intussusception with vascular compromise.

There were no significant differences between acute and convalescent measurements of plasma MDA, a circulating marker of lipid peroxidation and free radical activity. Free radical damage may well be important at a local level in intussusception or specifically in ischaemia–reperfusion injury but further investigations are needed to define the potential therapeutic role of free radical scavengers such as mannitol or allopurinol in children with acute intussusception.

Endotoxin, the lipopolysaccharide component of the cell wall of Gram-negative bacteria is toxic to humans in nanogram quantities. Lipid A is the main toxic moiety of endotoxin and is responsible for many of the pathophysiological responses leading to multiple organ failure in Gram-negative sepsis[12]. Although gut translocation of Gram-negative bacteria in intussusception was recognized many years ago[13], the role of endotoxin in this condition has been neglected. Previous investigation appears to have been limited to a mouse model of endotoxin-induced intussusception[14,15]. In the present study, all blood cultures were sterile but there was evidence of endotoxinaemia, particularly in children who needed intestinal resection. Endotoxinaemia may be an important factor influencing morbidity in intussusception.

IgG EndoCAbs are present at birth, probably as a result of maternal (transplacental) transmission[16]. Levels gradually decline over the first 3 months of life after which endogenous IgG EndoCAb begins to increase, reaching adult concentrations at about 6–7 years of age[5]. IgM EndoCAb (endogenous) is virtually absent in the first month of life but increases gradually to around adult levels by 1 year of age. Endotoxinaemia leads to an initial depletion in both IgG and IgM EndoCAb concentrations. Subsequently, the humoral anamnestic EndoCAb response may be triggered, and EndoCAb levels can rise rapidly[5]. The antibody responses observed in the children in the present study may indicate endotoxin exposure even where endotoxinaemia could not be measured. Acute IgM and IgG EndoCAb levels were relatively normal but IgM levels were significantly increased in convalescent sera. The time course of the endotoxin antibody response in adults, with IgM concentrations peaking around day 5–7 and IgG peaking around day 7–9, would be compatible with an endotoxin antibody response in children following acute intussusception, since convalescent samples were taken from most patients 2–6 days after the acute samples. The observation that depressed EndoCAb is associated with a poor clinical outcome in other clinical conditions[17–20] is compatible with the observation that children who required intestinal resection had the lowest acute IgM EndoCAb levels.

Acknowledgements

The authors are grateful to their paediatric surgical colleagues for permission to include their patients in this study.

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Original article

Totally extraperitoneal endoscopic repair of recurrent inguinal hernia

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Background: Conventional repair of recurrent inguinal hernia is associated with a re-recurrence rate as high as 35 per cent. Endoscopic mesh repair has promising results regarding both recurrence and complication rates.

Methods: In a retrospective review, the results of endoscopic totally extraperitoneal repair were evaluated in 104 patients with 108 recurrent hernias. Follow-up was at least 1 year. Type of recurrence, time of occurrence after previous repair, duration of surgery, complications, duration of hospital stay and number of re-recurrences were evaluated.

Results: Follow-up ranged from 12 to 29 (mean 16) months. Forty-three recurrences were direct, 41 indirect and 15 combined; one was a femoral hernia. Median time to previous operation was 36 months (range 8 days to 42 years). Median duration of surgery was 63 (range 25–160) min. While there were no complications during operation, 12 patients (12 per cent) had a postoperative complication. Two direct re-recurrences (2 per cent) occurred as a result of inadequate positioning of the prosthetic mesh.

Conclusion: The endoscopic totally extraperitoneal technique is safe and effective for the repair of recurrent inguinal hernia.

Paper accepted 11 February 2001

British Journal of Surgery 2001, **88**, 884–886

Introduction

While the recurrence rate after primary groin hernia repair, using an anterior approach without the use of mesh, is between 0·2 and 19 per cent[1], it may be as high as 30–36 per cent for recurrent hernia repair[2]. Because of earlier operation, the anatomy of the groin may be changed and scarring may hamper dissection[3]. Higher complication rates, such as ischaemic orchitis[4], and a higher morbidity are described for open recurrent hernia repair[5].

To avoid two aetiological factors in recurrence of an operated groin hernia, namely collagen deficiency[6] and tension on tissue[7,8], Stoppa *et al.*[9] described a new technique in 1984. It involved a synthetic prosthesis, introduced by an open anterior approach. Recurrence rates using this technique were significantly lower: 1·4 per cent reported by Stoppa and Warlaumont[10] and 0–7 per cent noted by others[11,12].

In the evolution of techniques towards minimally invasive surgery with theoretically less perioperative morbidity and a shorter rehabilitation, Ger *et al.*[13] described a method for laparoscopic implantation of prosthetic mesh. Although still controversial for primary hernias, the technique of endoscopic repair with a synthetic prosthesis has gained wide popularity for the repair of recurrent inguinal hernia[14]. This study investigated the feasibility and short-term results of the endoscopic totally extraperitoneal (TEP) technique in the repair of recurrent inguinal hernia.

Patients and methods

From July 1994 to July 1998, all patients with a recurrent inguinal hernia treated at the St Elisabeth Hospital, Tilburg were intentionally treated endoscopically by the TEP technique as described by McKernan and Laws[15]. Under general anaesthesia, through a subumbilical incision, balloon dissection was applied to develop the preperitoneal space without entering the abdominal cavity. Extensive lateral dissection, isolation and parietalization of the cord structures were performed under direct vision. A 10 × 15 cm polypropylene mesh was placed covering the myopectineal orifice, without fixation.

One hundred recurrent hernias were unilateral; four were bilateral. In the group of 104 patients, there were 100 men and four women of median age 58 (range 26–83) years. Of the 108 repairs, 87 followed one previous open anterior repair, 18 followed two previous repairs, one followed three and two followed four previous repairs.

Results

In 104 patients, the median interval between previous hernia repair and recurrence was 36 months (range 8 days to 42 years). Forty-three recurrent hernias were medial or direct, 41 were lateral or indirect and 15 were combined. One patient had a recurrent femoral hernia. In one patient the exact site of herniation could not be determined owing to the absence of the epigastric vessels after previous operation. In seven patients the site of herniation was not recorded.

The median duration of TEP repair was 63 (range 25–160) min. In five patients haemorrhage from the epigastric vessels occurred during dissection, which was controlled endoscopically by means of staples in all cases. Two operations (2 per cent) were converted to conventional open repair, one because of an iatrogenic peritoneal tear, which prevented sufficient distension of the preperitoneal space, and one because of extensive preperitoneal adhesions. In four other operations, the preperitoneal technique was switched intraoperatively to a transabdominal preperitoneal technique, because of unintended pneumoperitoneum.

The median hospital stay was 2 (range 1–11) days. Twelve patients (12 per cent) had a postoperative complication: two patients had a groin seroma, which required evacuation by needle puncture, two had a groin haematoma requiring surgical re-exploration, transient thigh numbness was seen in three patients, while one patient suffered hyperaesthesia suspicious of entrapment of the ilioinguinal nerve. Further complications included cystitis (n = 2), transient subcutaneous emphysema (n = 1) and subumbilical wound dehiscence (n = 1). There were no hernia-related deaths although one patient was lost to follow-up after he died from an unrelated cause.

The mean follow-up was 16 (range 12–29) months. Two patients developed further hernia recurrence. One occurred 10 months after endoscopic surgery and was caused by inadequate positioning of the prosthesis. The operation was performed in the first 6 months of the evaluation. This patient had laparoscopic reoperation by the transabdominal technique. Recurrence had developed in an area not covered by the mesh, just lateral to the pubic tubercle through Hesselbach's triangle. A second mesh was introduced endoscopically and positioned over the defect. The second re-recurrence occurred 12 months after endoscopic correction and also involved a defect on the medial side of the mesh. Correction was performed using the method of Stoppa *et al.*[9]. No further problems have occurred in these two patients.

Discussion

This study reports the results of a consecutive series of 104 patients with 108 endoscopically repaired recurrent inguinal hernias, with a minimum follow-up of 1 year, and describes a low re-recurrence rate and a low complication rate. Although the follow-up is relatively short, the low re-recurrence rate of 2 per cent is not expected to increase as recurrences after a posterior approach usually occur within the first 6 months after surgery, as the result of a technical error[16]. Both of the re-recurrences in this study were due to malpositioning of the prosthetic mesh and might partly be due to the effect of the learning curve[17].

Whereas the role of mesh implantation in primary hernia repair has been controversial, this technique has been widely accepted for the repair of recurrent hernias[14,18]. Besides mesh insertion by an open anterior approach, as described in 1975 by Stoppa *et al.*[19], which proved to be effective, laparoscopic mesh insertion has gained considerable popularity[20,21]. Of the different endoscopic techniques, the preperitoneal approach has particularly been advocated for recurrent hernia because it avoids the potential complications of intra-abdominal surgery[16]. It circumvents scar tissue from previous anterior operation and provides good visualization of the groin anatomy. The absence of scar tissue in the preperitoneal region should minimize the risk of injury to spermatic cord structures and the lateral cutaneous and genitofemoral nerves. Furthermore, there is no need to staple the prosthesis to the surrounding tissue, thus avoiding the risk of nerve injury[22].

The present study reports a very low recurrence rate for a corrected recurrent inguinal hernia (two of 108) and confirms other reports, describing a low morbidity and complication rate[16,23,24]. Other studies of the TEP technique for recurrent hernias are smaller. Knook *et al.*[25] reported seven re-recurrences in 35 recurrent hernia repairs with a mean follow-up of 43 months. Phillips *et al.*[26] described no recurrences in ten repairs with a follow-up of 12 months and Memon and colleagues[2] mentioned none in eight repairs with a median follow-up of 27 months. Felix *et al.*[3] described one re-recurrence in a series of 90 recurrent hernias, with a follow-up of 89 per cent after 14 months, but it is not quite clear whether this operation was performed using the TEP technique or the transabdominal preperitoneal (TAPP) technique.

Regarding the TAPP technique for recurrent hernia, larger series are reported: Sandbichler *et al.*[22] reported one re-recurrence in 200 repairs (0·5 per cent), but this study had a follow-up of only 54 per cent after 1 year. Deans and colleagues[27] described no re-recurrences in ten repairs with a median follow-up of 6 months and Memon *et al.*[2] noted two in 68 recurrent hernia repairs with a follow-up of 27 months. Some other studies reported very low recurrence rates for endoscopic mesh repair[16,28], but these did not differentiate between the results of primary or recurrent hernia repairs. In all these studies, the majority were primary hernias. Some cite a significantly higher recurrence rate for the TAPP technique. Beets *et al.*[29], for example, reported seven recurrences in 56 both primary and recurrent hernias (13 per cent).

The median hospital stay of 2 days in the present series is explained by the policy of keeping patients in hospital overnight after surgery. Recently the operation has been done as a day case.

Endoscopic totally preperitoneal prosthetic mesh insertion is a safe and effective technique for the repair of recurrent inguinal hernia.

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Correspondence

The Editors welcome topical correspondence from readers relating to articles published in the Journal. Letters should be no more than 250 words in length and should be typed on A4-sized paper in double spacing

Major intra-abdominal pathology missed at laparoscopic cholecystectomy (*Br J Surg* 2000; 87: 1434–5)

Sir

Malouf *et al.* advocate a policy of routine thorough diagnostic laparoscopy at the time of laparoscopic cholecystectomy. This is based on their finding of four cancers (two colonic and two periampullary) in 695, presumably consecutive, patients undergoing laparoscopic cholecystectomy. Unless a thorough laparoscopy of the lesser sac is carried out it would be difficult to diagnose periampullary cancers in patients who are not jaundiced. This would add time to laparoscopic cholecystectomy and we know that operating theatre time is the largest cost bearer of this procedure, amounting to up to 60 per cent of the total hospital expense[1]. Adding even 10 min for diagnostic laparoscopy would add 6950 min of operating time in these cases, or in other words at least 14 full day operating lists in the Lothian region. Can we afford it both in terms of time and cost? Would a managerial driven health care system allow this expensive diagnostic modality with a pick-up rate of 0·6 per cent, or are better preoperative or postoperative algorithms required for patients with atypical symptoms and gallstones? While randomized controlled trials have proven the value of diagnostic laparoscopy in the acute setting, the issue has yet to be fully resolved in the patient with chronic abdominal pain[2].

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Chronic dysphagia following laparoscopic fundoplication (*Br J Surg* 2000; 87: 1341-5)

Sir

We have performed a similar study to Bessell *et al.* comparing Nissen fundoplication with anterior partial fundoplcation in patients with both normal and abnormal oesophageal motility. One hundred and seven patients with gastro-oesophageal reflux disease were randomized to undergo either Nissen fundoplication (53) or anterior 180° hemifundoplication (54), and follow-up was obtained at least yearly by a blinded investigator using standardized clinical grading systems to assess postoperative dysphagia, heartburn and patient satisfaction. Patients were divided into two groups depending on their preoperative oesophageal manometry: normal peristalsis (81 patients) or disordered peristalsis (26 patients; propagated < 50 per cent of swallows and/or distal peristaltic amplitude < 40 mmHg). At all follow-up intervals beyond 6 months, patients undergoing anterior fundoplication experienced less dysphagia and were more likely to be satisfied with the outcome. However, the magnitude of the outcome differences was independent of peristaltic status and there was no trend towards a poorer outcome in patients with poor peristalsis undergoing Nissen fundoplication. Our findings were similar to those of Bessell *et al.* and did not support the concept of tailoring antireflux surgery according to preoperative peristaltic status. However, laparoscopic anterior fundoplication was associated with less dysphagia overall and an improved clinical outcome at 3 years.

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Short-term results of femoropopliteal subintimal angioplasty (*Br J Surg* 2000; 87: 1361-5)

Sir

Although this study was well conducted, I believe the final conclusion of a poor clinical success rate contradicts the study results. From the data, one can conclude that in critical ischaemia there is an initial success rate of 72 per cent for this technique. This may not sound too good to those unfamiliar with the technique, but this is a simple benign procedure[1]. All manipulation, which in experienced hands takes no more than 30 min, is through a 5 French sheath and can even be performed on an outpatient basis. Failure, if one considers the general vascular and medical status of the patient, is only relative. Even if one is successful in only 72 per cent of patients, the gain for this specific type of patient is high. I should like to raise the following question: what will be the clinical outcome for a 75-year-old patient with critical lower leg ischaemia unsuitable for operation due to co-morbidity or an unfavourable disease pattern (inclusion criteria for this study) at 8 months? According to McCarthy *et al.* a good outcome would occur in 83 per cent of all patients undergoing the extraluminal procedure. I would conclude that the management of patients with critical ischaemia with an unfavourable surgical option is percutaneous intentional extraluminal recanalization. Only those whose treatment fails will face, according to McCarthy *et al.*, a gloomy future which is, however, unrelated to this treatment.

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1 Reekers JA, Bolia A. Percutaneous intentional extraluminal (subintimal) recanalization: how to do it yourself. *Eur J Radiol* 1998; **28:** 192–8.

Anatomy of Denonvilliers' fascia and pelvic nerves, impotence, and implications for the colorectal surgeon (*Br J Surg* 2000; 87: 1288-99)

Sir

Lindsey *et al.* provide a comprehensive account of the detailed anatomy of Denonvilliers' fascia and pelvic innervation, and outline their importance to colorectal surgeons, particularly with respect to male impotence. There are some aspects of female anatomy that may be apposite in this context.

As is indicated by the authors, the macroscopic appearances of Denonvilliers' fascia vary. Parity may be important since there are few, if any, studies of either anterior or posterior pelvic compartments in nulliparous subjects.

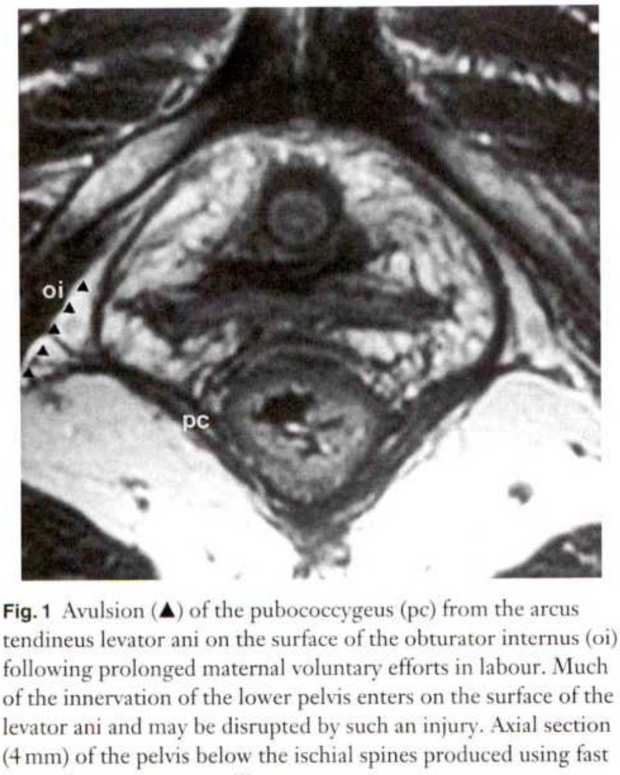

Fig. 1 Avulsion (▲) of the pubococcygeus (pc) from the arcus tendineus levator ani on the surface of the obturator internus (oi) following prolonged maternal voluntary efforts in labour. Much of the innervation of the lower pelvis enters on the surface of the levator ani and may be disrupted by such an injury. Axial section (4 mm) of the pelvis below the ischial spines produced using fast spin echo sequences, 1·5T.

The primary importance of the posterior axis of support, where the uterosacral-cardinal ligament complex suspends the rectovaginal septum and posterior vaginal wall to the perineal body, is often understated.

The uterosacral ligaments insert primarily into the posterosuperior vagina (rather than the uterine cervix) and deliver significant neurovascular bundles. These nerve fibres have not been extensively studied although do appear to contain parasympathetic fibres[1].

Avulsion of the origin of the levator ani (*Fig. 1*) consequent upon premature, or prolonged, maternal voluntary efforts in labour disrupts nerves entering the pelvis on its surface which may cause sensory symptoms (pelvic pain, deep dyspareunia, urinary urge incontinence, faecal urgency) in the medium term by an allodynic mechanism.

Division of the uterosacral ligaments at hysterectomy and some forms of vaginal delivery may have significant consequences for the innervation of the rectum. We would not presume to speculate as to how this damage might present to colorectal colleagues although they might agree that obstetricians and gynaecologists could reflect on their role in the development of these problems.

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1 Campbell RM. The anatomy and histology of the sacrouterine ligaments. *Am J Obstet Gynaecol* 1950; **59:** 1–12.

Vascular access for haemodialysis (*Br J Surg* 2000; 87: 1300-15)

Letter 1

Sir

The authors stress the importance of construction of distal arteriovenous fistulas (AVFs) in the arms first, preserving more proximal sites for subsequent procedures. They fail to mention the anatomical snuffbox as the most distal site in the arm. The surgical technique and patency rates (equal to those of the classic Brescia-Cimino radiocephalic AVFs) are well documented[1–3].

The proximity between the radial artery and cephalic vein in the anatomical snuffbox allows easy anastomosis without mobilization and transposition of the vein. Once matured the snuffbox fistula offers a long segment of vein for needling. Due to the small calibre of the artery the risk of developing a steal phenomenon or cardiac failure is minimized. In 376 primary vascular access procedures the construction of a snuffbox AVF was possible in 187 patients (50 per cent)[3]. When a snuffbox fistula failed an ipsilateral radiocephalic AVF could be constructed at the wrist in 45 per cent of patients. This may reduce the subsequent need for prosthetic grafts (only 18 out of

645 access procedures over 12 years). Despite its infrequent use in the UK, the snuffbox AVF is certainly worth considering in patients requiring long term vascular access for haemodialysis.

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1 Bonalumi J, Civalleri D, Rovida S, Adami GF, Gianetta F, Griffanti-Vartoli F. Nine years' experience with end-to-end arteriovenous fistula at the 'anatomical snuffbox' for maintenance haemodialysis. *Br J Surg* 1982; **69:** 486–8.
2 Marx AB, Landman J, Harder FH. Surgery for vascular access. *Curr Probl Surg* 1990; **27:** 1–48.
3 Wolowczyk L, Williams AJ, Donovan KL, Gibbons CP. The snuffbox arteriovenous fistula for vascular access. *Eur J Vasc Endovasc Surg* 2000; **19:** 70–6.

Letter 2

Sir

The number of patients needing renal replacement is increasing every year because of an ageing population and improvements in haemodialysis may allow patients to live longer on such replacement therapy. The disparity between the number of organs available and the number of patients on the transplant waiting list simply means patients will spend a long time on haemodialysis. This large patient population inevitably often needs secondary and tertiary procedures for continued safe vascular access.

This article exposes the situation quite clearly; there is much to do. Data are lacking from which clinicians might learn and formulate management protocols. Is there a need to set up a central databank on the lines of the colorectal or breast cancer registries? The Renal Association and the nephrologists have as much at stake here as the surgeons. A good fistula done at the right time and looked after well goes a long way in reducing morbidity. This happens only if patients with deteriorating renal function are referred at the right time, so that they have a functioning fistula when they need dialysis. This cuts down the problems associated with acute admissions and urgent central vein cannulation.

A multidisciplinary approach, as the authors highlight, together with a facilitator, such as a vascular access co-ordinator[1] who could liaise between the specialities, would greatly improve the service to our patients. Our own experience in Liverpool is similar to that of Allon *et al.*[1]. Is there a need for such a person to be employed by renal units nation-wide to improve access services?

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1 Allon M, Bailey R, Ballard R, Deierhoi MH, Hamrick K, Oser R *et al* A multidisciplinary approach to haemodialysis access: prospective evaluation. *Kidney Int* 1998; **53:** 473–9.

Role of resection and primary anastomosis of the left colon in the presence of peritonitis (*Br J Surg* 2000; 87: 1580-4)

Sir

This study was reported to be prospective in nature but in the latter part of the study, because of the increasing confidence with the technique and the good results, resection and primary anastomosis (RPA) was offered to selected patients with diffuse peritonitis. Could this produce a selection bias and render comparison between the outcome in patients with localized and diffuse peritonitis invalid? Two patients who were immunocompromised also underwent RPA and this was an exclusion criterion. The number of patients and the location of disease in patients with complicated non-specific, inflammatory disease who were excluded from this study are not clear. The readers will be keen to know the location of the perforation in the 13 patients with carcinoma as the morbidity of surgery is different for a low anterior resection *versus* a sigmoid colectomy. This assumes more significance as the authors did not fashion any covering stoma at all. Did those patients who needed more technically demanding procedures undergo Hartmann's procedure in preference to RPA and covering stoma? Were these anastomoses hand-sewn or stapled?

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Suitability for endovascular aneurysm repair in an unselected population (*Br J Surg* 2001; 88: 77–81)

Sir

Woodburn *et al.* make much of the difference between their own series and those from tertiary referral centres. The results are in fact not dissimilar. Their figures are selectively interpreted to support their conclusion that the proportion of abdominal aortic aneurysms (AAAs) suitable for endovascular repair is lower than suggested previously by centres like our own[1].

The seven patients with thoracoabdominal aneurysms and one with a ruptured aneurysm should not have been included in the AAA series. Five aneurysms, which though suitable, are then excluded on surgical grounds for being less than 5·5 cm in diameter and asymptomatic. We are not told how many of the unsuitable AAAs were also less than 5·5 cm and asymptomatic. If the first group of patients are excluded and the latter included, 49 per cent (52 of 107) are found to be suitable for an aortouniiliac graft and 36 per cent (39 of 107) for a bifurcated graft. This compares with our figures in 1997 of 55 and 10 per cent.

Figures for suitability depend largely on where the anatomical boundaries are drawn, and these in turn are influenced by the device, operator experience and passage of time. The study by Woodburn *et al.* confirms the representativeness of our own anatomical database (in which tertiary referrals had the same spread of anatomical features as those from the local practice). The small difference in our figures for the aortouni-iliac device is probably due to our neck diameter limit being set at 3 cm compared to the limit set by the authors of 2·8 cm.

We would suggest this paper has actually demonstrated a greater than three-fold increase in the numbers of patients that are suitable for repair with commercially available endovascular devices. This represents significant graft evolution in only 4 years and a study 5 years from now may well conclude that the majority of AAAs can be treated by endovascular means.

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1 Armon MP, Yusuf SW, Latief K, Whitaker SC, Gregson RHS, Wenham PW *et al.* The anatomical suitability of abdominal aortic aneurysms for endovascular repair. *Br J Surg* 1997, **84:** 178–80.

Authors' reply

Sir

While we acknowledge the significant contribution made by the Nottingham group in the development of endovascular abdominal aortic aneurysm (AAA) repair we cannot agree with their interpretation of our results. Our series consisted of all patients referred to a single vascular surgical service for consideration of elective aneurysm repair. The diagnosis of AAA had been made on clinical and/or ultrasonographic examination. On initial assessment by a vascular surgeon it was considered appropriate to investigate these patients further as described, with the intention of undertaking repair of their AAA. Exclusion of those patients subsequently identified as having aneurysmal disease extending above the renal arteries or a contained leak would have introduced the element of selection that we believe has influenced some reports to overestimate the applicability of endovascular repair.

Armon and colleagues also suggest including those aneurysms that, while morphologically suitable for endovascular repair, did not meet currently accepted criteria for conventional surgical repair[1]. It has been suggested that endovascular repair may have a wider role if the threshold for surgical intervention were lowered[2]. This remains controversial and until current concerns regarding the durability of endovascular repair have been dispelled, it is our contention that, even if morphologically suitable, asymptomatic aneurysms of less than 5·5 cm diameter are not appropriate for such surgery. While commercially available endovascular devices will evolve to treat an increasing number of aneurysms, at the present time we still believe that only one-third of patients are appropriate for endovascular repair after formal assessment.

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1 Mortality results for randomised controlled trial of early elective surgery or ultrasonographic surveillance for small abdominal aortic aneurysms. The UK Small Aneurysm Trial Participants. *Lancet* 1998; **352:** 1649–55.

2 May J, White GH, Yu W, Waugh R, Stephen M, Harris JP. Concurrent comparison of endoluminal repair *versus* no treatment for small abdominal aortic aneurysms. *Eur J Vasc Endovasc Surg* 1997; **13:** 472–6.

Probiotics (*Br J Surg* 2001; 88: 161–2)

Sir

I should like to update O'Sullivan's excellent editorial on probiotics by providing some additional data reported in a recently published study. In a randomized trial 32 patients with Crohn's disease in remission were allocated to a maintenance treatment with either mesalazine 3 g daily or mesalazine 2 g daily plus a preparation of *Saccharomyces boulardii* (two 500 mg capsules in the morning). At 6 months clinical relapses were found to be significantly less frequent in the group which, in addition to standard mesalazine maintenance, received the probiotic agent[1]. These results support the general concept that probiotics can be useful in the treatment of inflammatory bowel disease and suggest that *Saccharomyces boulardii*, in particular, is a micro-organism able to exert anti-inflammatory effects in the intestinal environment. Further studies are in progress to confirm and enlarge these preliminary data. Interestingly, antibodies against *Saccharomyces cerevisiae*, a closely related yeast, are frequently detectable in patients with Crohn's disease[2]. The possible relationship between the presence of those antibodies and the therapeutic response to *Saccharomyces boulardii* is currently under investigation.

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1 Guslandi M, Mezzi G, Sorghi M, Testoni PA. *Saccharomyces boulardii* in maintenance treatment of Crohn's disease. *Dig Dis Sci* 2000; **45:** 1462–4.

2 Quinton JF, Sendid B, Reumaux D, Duthilleul P, Cortot A, Granbastien B *et al.* Anti-*Saccharomyces cerevisiae* mannan antibodies

combined with antineutrophil cytoplasmic autoantibodies in inflammatory bowel disease. prevalence and diagnostic role. *Gut* 1998; **42**: 788–91.

Prospective evaluation of the morbidity of axillary clearance for breast cancer (*Br J Surg* 2001; 88: 114–7)

Sir

In the Ulster Hospital Breast Unit all patients undergoing axillary surgery for malignant breast disease are counselled preoperatively about postoperative shoulder mobility, lymphoedema and other potential complications. Intensive exercise regimens are commenced on the day after operation, with physiotherapy twice daily. Patients are encouraged to perform their exercises every hour. Those who do not regain preoperative shoulder mobility before leaving hospital are reviewed on alternate days following discharge until movements are restored to normal. Patients are advised to continue the exercise regimens for 6 weeks.

We have recently completed a study evaluating shoulder mobility, lymphoedema and other complications on 121 patients (median follow-up 24 months). Our lymphoedema rate, although assessed differently, appears similar to that of Duff *et al.* with 3 per cent of patients having significant lymphoedema (an increase in arm volume of greater than 5 per cent persisting longer than 6 months). However, the median time for return to full range of shoulder movement was 6 days (range 2–24) and all patients regained shoulder mobility to preoperative levels. Five women (4 per cent) required more than 2 weeks to complete this process. No functional arm problems were noted at initial surgical outpatient review, 3 months after treatment. We believe that appropriate aggressive physiotherapy regimens with adequate analgesia can significantly reduce the morbidity associated with arm movement following axillary surgery.

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Jejunal interposition to prevent postgastrectomy syndromes (*Br J Surg* 2000; 87: 1576–9)

Sir

We agree with the authors about the occurrence and significance of 'Roux-en-Y stasis syndrome' (RSS) following gastrectomy. Beside Roux loop dysmotility, the size of the gastric remnant and disturbed postoperative gastric motility play an important part in the symptomatology of RSS[1,2]. The present study does not address the importance of these two factors. The beneficial effect of more extensive gastric resection reduces the morbidity caused by RSS[2].

In the 'uncut' Roux-en-Y anastomosis neuromuscular continuity is maintained. In a prospective randomized controlled trial involving 51 patients Noh demonstrated that this procedure significantly reduces the incidence of RSS[3]. The present study is a non-randomized comparative case-centred study with a follow-up period of 12 months. The authors have compared patients undergoing Billroth I gastrectomy with jejunal interposition procedure and concluded that it effectively prevented postgastrectomy functional syndrome, which we think is misleading.

Further studies incorporating all three techniques are needed with long-term follow up. Until then it is our view that the traditional Roux-en-Y should remain the first choice after subtotal gastrectomy.

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1 Schirmer BD. Gastric atony and the Roux syndrome. *Gastroenterol Clin North Am* 1994; **23**: 327–43.
2 Hinder RA, Esser J, DeMeester TR. Management of gastric emptying disorders following the Roux-en-Y procedure *Surgery* 1988; **104**: 765–72.
3 Noh SM. Improvement of the Roux limb function using a new type of 'uncut Roux' limb. *Am J Surg* 2000, **180**: 37–40.

Author's reply

Sir

We investigated the advantages of jejunal interposition procedure compared with Billroth I repair but did not evaluate the Roux-en-Y reconstruction. Roux-en-Y reconstruction is technically simple to construct and effective in preventing alkaline reflux gastritis. Disadvantages include 'Roux-en-Y stasis syndrome' and nutrient malabsorption. The lack of mixing of chyme and pancreaticobiliary secretions may cause nutrient malabsorption, such as deficiency of iron, vitamin B_{12} and folic acid in long-term follow-up[1]. Jejunal interposition procedure allows a physically more correct route for food. This procedure does have an increased operating time, but we did not encounter serious postoperative complications. We recommend jejunal interposition procedure following distal gastrectomy but agree that further studies are needed which incorporate all three techniques and with long-term follow up.

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1 Avinoah E, Ovnat A, Charuzi I. Nutritional status seven years after Roux-en-Y gastric bypass surgery. *Surgery* 1992; **111**: 137–42.

General Surgery Outpatient Decisions

M. E. Gaunt

215 × 138 mm. Pp 374 2000. London Arnold £22·50

This book is aimed at senior house officers and junior registrars faced with the prospect of their first surgical speciality clinics. The author's main aim is to describe a reasonable line of management suitable for most patients that can be modified to take account of patient and local factors. A further aim is to prevent unnecessary follow-up of review patients who are often dealt with by a succession of trainees. Part one explores the general issues of the consultation. It provides practical guidance on how to conduct an outpatient consultation, from planning and structuring and determining the objectives, through to dictating the letter. Part two comprises ten chapters that give a general overview of the relevant surgical speciality, followed by more detailed discussion of specific conditions and investigations. The salient points of history and examination are emphasized, along with the appropriate investigations (including techniques and their limitations, and how best to complete request forms). Treatment and timing of follow-up are discussed, and when to seek senior advice is clearly emphasized, as is the importance of good communication with the patient, relatives and other healthcare professionals. The book is easy to read and assumes a basic level of knowledge. However, it is short on tables and has no flow diagrams or illustrations. There is certainly a gap in the market for a book aimed at improving knowledge and reducing anxiety in an area where formal teaching is often lacking. In the less than ideal situation of limited senior cover, this book provides advice for a safe course of action for all common surgical conditions.

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Surgery: Basic Science and Clinical Evidence

J. A. Norton, R. R. Bollinger, A. E. Chang, S. F. Lowry, S. J. Mulvihill, H. I. Pass, R. W. Thompson (eds)

282 × 222 mm Pp 2170 Illustrated 2000 New York Springer £68·50

This large and extensively referenced tome covering all aspects of surgery has, in today's world of evidence based medicine, a most inviting title. The fact that the editorial board did not commence their project until 1997 and in the meantime have been able to put together a surgical textbook of over 2000 pages, 93 chapters and 200 evidence based tables, is of immense credit to all concerned. It also comes with an impressive compact disc containing the references for each chapter along with a direct link (for most) to a detailed abstract. According to the senior editor the aim of the book was to assemble current and future leaders in surgery who would put together an evidence based surgical textbook, providing the reader with the most up-to-date and relevant information on which to base decisions in modern surgical practice. Have they been successful? The answer is a tentative yes, but with a few provisos. There is no doubt that this text provides reasonably up-to-date information in all the surgical specialities in a clear and concise style with extensive referencing. In the interpretation of the data, however, it does tend to favour current practice in North America; this is hardly surprising since all but four authors come from the USA or Canada.

The main problem with such large surgical texts is that by the time of publication new data has appeared in the literature resulting in many opinions becoming outdated. With all the current interest in evidence based medicine, publication of randomized controlled clinical trials and meta-analyses, this book unfortunately also suffers, despite the relatively short time between conception and publication. Although all the authors have tried hard to put together as much evidence as possible in support of the opinions expressed in their individual chapters, there are several areas that would already benefit from updating. In relation to the actual content there are some surprising statements that cannot be supported by current evidence, such as the recommendation that (when feasible) parietal cell vagotomy is the operation of choice for peptic ulcer disease. Although this may be true in the USA it is certainly not the case in the UK. There is no mention of the results of many trials over the last decade reporting both adjuvant and neo-adjuvant chemotherapy, radiotherapy and chemoradiotherapy for oesophagogastric cancer. Furthermore, the recommendation that patients with locally resectable stage IV oesophageal carcinoma should undergo palliative resection would certainly not find much support on this side of the Atlantic. It is also disappointing to see that the more up-to-date staging classification regarding nodal status for gastric cancer is not mentioned, despite being published in 1997. In the management of obstructing left-sided colonic carcinoma, no mention is made of on-table washout and left-sided resection with primary anastomosis, the authors preferring to recommend subtotal colectomy and primary anastomosis as the best option. This is despite a randomized controlled trial in the literature supporting the longer-term results from the former procedure. However, all surgical texts tend to reflect the bias and opinions of the authors and, overall, these criticisms should not detract too much from an extremely well written, informative and extensively referenced textbook, which has certainly stolen a march on the competition.

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Handbook of Breast Surgery

A. S. Ball, P. M. Arnstein

214 × 138 mm Pp. 166 Illustrated 1999. London. Arnold £24·99

This book is ideal for a specialist registrar who is attached to a breast centre or unit. It is didactic, clear, the majority is in brief note form, readily memorable and an easy reference, making it ideal for revision purposes. There are a considerable number of controversies in breast surgery and I think the text lacks balance with regard to the use of drains, the lack of mention of day surgery for breast conservation and axillary sampling (which is now widely practised) and the fact that wire guided localization is often carried out as a therapeutic manoeuvre and therefore the breast weight does not have to be under 20 g (as stated in chapter six). The text on gynaecomastia is an over-simplification. It is important for all trainees to realize that a subcutaneous mastectomy when there is a degree of ptosis leads to a very poor result. Table 11·2 could be improved in future editions by highlighting the salient figures. These are minor criticisms and do not detract from the overall clarity.

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Phlebology: The Guide

A. A. Ramelet, M. Monti

224 × 142 mm Pp. 445. Illustrated. 1999 Amsterdam: Elsevier $30·00.

When the discipline of phlebology is barely acknowledged to exist in the English speaking world, this book is a welcome step to opening up the European perspective on this subject. It comes in a concise and well presented textbook, that is in its fourth edition but has for the first time become available in English. The contributions come from a group of experienced Swiss specialists presenting their expert views, with only one surgeon among them. The focus is clinical and descriptive in a traditional style, with good use of coloured illustrations. The European clinical classifications and descriptions are useful, for instance types of oedema-phlebedema, lymphoedema and lipedema.

This book is especially helpful for surgeon readers of the *BJS* because it opens up the full scope of venous disease and its management. There are perspectives in the clinical presentation and treatment of varicose veins that are readily neglected by those with a single surgical focus. This book helps to broaden that focus and should enhance patient care. Having the perspectives of a phlebologist, a dermatologist, an angiologist, a radiologist as well as a surgeon wrapped up together has advantages. Chapters that include physical therapy, life style issues and drug therapy are a reminder that there may be more to offer. There is information worth knowing about phlebotrophics and oedema protective agents, both of which are widely used by angiologists. However, the principles of evidence based medicine are not critically applied. Still, as the authors point out 'the efficiency of phlebotrophics has often been contested, but it is never the less well established' and 'despite being extensively researched in Europe they are usually not discussed in textbooks…'. For the surgeon reader these European differences should not be a distraction. There is a lot of good surgical information, day care phlebectomy for example. This textbook is up-to-date, sound and provides a practical overview. For the general surgeon or trainee, for whom varicose veins or phlebology is a common problem in their practice, this book is well worth delving into.

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The Complete MRCS: Volumes 1 and 2

J. K. C. Huang, M. C. Winslet (eds)

215 × 136 mm Volume 1 pp 216 Volume 2 pp. 240. 2000 Edinburgh Churchill Livingston. £16 95 each

The Complete MRCS texts contain multiple choice questions (MCQs) and extended matching questions (EMQs) with answers, and are aimed at surgical trainees preparing for the Membership of the Royal College of Surgeons (MRCS) Part 1 examination in the UK. It is closely allied to the syllabus laid out in the Surgeons in Training Education Programme (STEP) course and this is reflected in the way the chapters are divided. The layout of the book is clear and concise with MCQs and EMQs in proportions appropriate to the MRCS examination, covering both clinical and basic science topics. The questions cover a wide range of subjects within the structure of the STEP course and have suitable scope and detail to reflect the level of knowledge required to pass the MRCS Part 1. Syntax and grammar similar to that found in the exam has been adopted. The answers are set out at the back of each book. The authors have included suitably detailed explanations and relevant discussions without being longwinded. In my opinion these books are a good test of the basics, and are useful for consolidating pre-existing knowledge. They give a good flavour of the type of questions that occur in the Part 1 examination, laid out in a clear and easy to read package.

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Scientific Surgery

The *BJS* is committed to the practice of surgery based on scientific evidence. Each month we will publish a list of randomized trials and meta-analyses collated from English-language publications. A collection of all these papers will be available in the Scientific Surgery Archive which will be held on the *BJS* website together with links to free Medline sites where the full papers can be accessed (see below for details). If you have published a recent randomized trial which has not been featured in Scientific Surgery, the Editors would be pleased to receive a reprint and consider its inclusion.

Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group. Low dose dopamine in patients with early renal dysfunction: a placebo-controlled randomized trial. *Lancet* 2000; **356**: 2139–43.

This multicentre trial included 328 patients in an intensive care unit. Treatment with low-dose dopamine had no effect on measured renal function, survival or any other of the clinical parameters measured.

Rink AD, Goldschmidt D, Dietrich J, Nagelschmidt M, Vestweber KH. Negative side-effects of retention sutures for abdominal wound closure. A prospective randomized study. *Eur J Surg* 2000; **166**: 932–7.

Wire deep tension sutures were randomly allocated in 95 high-risk patients who had a laparotomy. The sutures increased postoperative pain, and 21 of 44 had to be removed prematurely.

Rock CL, Thomson C, Cann BJ, Flatt SW, Newman V, Ritenbaugh C *et al.* Reduction in fat intake is not associated with weight loss in most women after breast cancer diagnosis. *Cancer* 2001; **91**: 25–34.

One thousand women with breast cancer were randomized to dietary advice by telephone or given written advice. Mean weight increase in 1 year was 0·04 and 0·46 kg, respectively, though the majority of women had stable weight

Evans J, Luck A, Hewett P. Glyceryl trinitrate *versus* lateral sphincterotomy for chronic anal fissure: prospective randomized trial. *Dis Colon Rectum* 2001; **44**: 93–7.

After 8 weeks, 61 per cent of fissures healed after glyceryl trinitrate compared with 97 per cent after surgery ($P < 0·001$) in this study of 65 patients Twelve patients in the glyceryl trinitrate group later underwent surgery

Milsom JW, Hammerhofer KA, Böhm B, Marcello P, Elson P, Fazio VW *et al.* Prospective, randomized trial comparing laparoscopic *versus* conventional surgery for refractory ileocolic Crohn's disease. *Dis Colon Rectum* 2001; **44**: 1–9.

All the 60 patients studied recovered after surgery. Two laparoscopic procedures were converted to open Minor complications were more common after open surgery. Analgesic requirements were similar, as was duration of hospital stay (median 5 days for laparoscopic *versus* 6 days for open surgery)

Cales P, Masliah C, Bernard B, Garnier P-P, Silvain C, Szostak-Talbodec N *et al.* Early administration of vapreotide for variceal bleeding in patients with cirrhosis. *N Engl J Med* 2001, **344**: 23–8.

Some 227 patients with cirrhosis and bleeding were randomized to vapreotide or placebo followed by endoscopic intervention. Overall survival at 42 days was similar, but survival with control of bleeding (the primary objective) was more likely after vapreotide (66 *versus* 50 per cent, $P = 0·02$).

Fujii Y, Tanaka H, Kawasaki T. Prophylaxis with oral granisetron for the prevention of nausea and vomiting after laparoscopic cholecystectomy. A prospective randomized study. *Arch Surg* 2001; **136**: 101–4.

In this trial including 120 operations, granisetron significantly reduced the risk of postoperative vomiting at different doses as follows: from 47 per cent with placebo to 40 per cent after 1 mg, and 17 per cent after 2 mg or 4 mg ($P = 0·01$)

Yerdel MA, Akin EB, Dolalan S, Turkcapar AG, Pehlivan M, Gecim IE *et al.* Effect of single-dose prophylactic ampicillin and sulbactam on wound infection after tension-free inguinal hernia repair with polypropylene mesh: the randomized, double-blind, prospective trial. *Ann Surg* 2001; **233**: 26–33.

In this trial including 280 operations, the wound infection rate was reduced from 9 to 0·7 per cent by antibiotic prophylaxis ($P = 0·0015$) The mesh was removed for infection in two patients.

López-Beret P, Orgaz A, Fontcuberta J, Doblas M, Martinez A, Lozano G *et al.* Low molecular weight heparin *versus* oral anticoagulants in the long term treatment of deep venous thrombosis. *J Vasc Surg* 2001; **33**: 77–90.

Some 158 patients were randomized to one of two different anticoagulant schedules for 3 to 6 months. During the following 12 months patients in the low molecular weight heparin group had a significantly increased rate of vein recanalization and reduced the rate of superficial and deep incompetence The risk of recurrent deep venous thrombosis was not reduced significantly (2 5 *versus* 9 per cent).

Daniele B, Perrone F, Gallo C, Pignata S, De Martino S, De Vivo R *et al.* Oral glutamine in the prevention of fluorouracil induced intestinal toxicity: a double blind, placebo controlled, randomized trial. *Gut* 2001; **48**: 28–33.

In this study including 70 patients with colorectal cancer, the addition of glutamine significantly reduced the severity of the diarrhoea and the requirement for loperamide.

The *BJS* website can be found at *www.bjs.co.uk*. In addition to details of current and previous articles featured in Scientific Surgery, the website contains details of the Editorial Team and Board, instructions to prospective authors, links to other sites (such as The Cochrane Library) and forthcoming surgical events. The Editors welcome comments and suggestions about the website, either in writing or through the website address.

Instructions to authors

BJS publishes original articles, reviews and leading articles all of which are submitted to peer review.

An article is reviewed for publication assuming that its contents have not been submitted simultaneously to another journal, have not been accepted for publication elsewhere and have not already been published. **Any attempt at dual publication will lead to automatic rejection and may prejudice acceptance of future submissions.** Please submit with your manuscript copies of any other papers (published, in press, or submitted for consideration elsewhere) that relate to the same subject. It is essential that you submit any other publications or submissions that use the same data set to allow assessment of any potential overlap. Indicate on the title page whether the paper is based on a previous communication to a society or meeting. Articles and their illustrations become the property of the Journal unless rights are reserved before publication.

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A covering letter must accompany all submissions, must be signed by all authors and must state whether an abstract of the work has been published - please provide an appropriate reference. Disclose in the covering letter any potential or actual personal, political or financial interest you may have in the material, information or techniques described in the paper. The Journal takes very seriously its obligation to assess and declare any actual or potential conflicts of interest. The decision to publish or withhold such information will be made by the Editors. Acknowledge all sources of financial support. The first named author is responsible for ensuring that all authors have seen, approved and are fully conversant with its contents. The Journal accepts the criteria for authorship proposed in the *British Medical Journal* (*BMJ* 1994; **308**: 39–42). If a paper has more than six authors you should justify the inclusion of all names. Results of multicentre studies should be reported under the name of the organizing study group. Methods of recognizing contributors have been proposed (*Lancet* 1995; **345**. 668).

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IBM-compatible disks would be preferred (3½ inch). An accurate hard copy must accompany each disk, together with details of the type of computer used, software and disk system. **Do not justify.** Please send us digital versions of your figures. Ideally these should be sent in native format or WMF if created in Windows. Files saved as PS, EPS, GIF and TIF may also be used, but please note that it may not be possible to modify them. Disks will not be returned to authors.

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Ethics

Material relating to human investigation and animal experiments must comply with and be approved by local ethics committees. It must conform to standards currently applied in the country of origin. The Journal reserves the right not to publish an article on the grounds that appropriate ethical or experimental standards have not been reached. Written consent must be obtained from the patient, legal guardian or executor for publication of any details or photographs that might identify an individual. Submit evidence of such consent with the manuscript.

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BJS subscribes to the policy of uniform requirements for manuscripts which facilitates resubmission of papers to journals without extensive recasting. Authors are advised to consult the *New England Journal of Medicine* (*N Engl J Med* 1997; **336**: 309–15), or obtain 'Uniform Requirements for Manuscripts Submitted to Biomedical Journals' from The Editor, *British Medical Journal*, BMA House, Tavistock Square, London WC1H 9JR, UK (cost £2 95 per copy).

Authors are responsible for the accuracy of their report including all statistical calculations and drug doses. **When quoting specific materials, equipment and proprietary drugs you must state in parentheses the brief name and address of the manufacturer.** Generic names should normally be used.

Original articles

Original articles should normally be in the format of introduction, patients and methods, results and discussion. Please provide a 200-word structured abstract. Lengthy manuscripts will be returned for shortening. The discussion in particular should be clear and concise and limited to matters arising directly from the results Avoid discursive speculation. **Randomized clinical trials** should be clearly identified as such in the title and abstract.

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The Editorial Board of the *BJS* encourages submission of review articles or meta-analyses on topics of interest. Any topic will be considered, but priority will be given to those addressing a major current problem. The author of each accepted article will receive an honorarium. Before submission of a meta-analysis of randomized trials, authors are encouraged to consult the QUORUM statement, designed to assist in improving the quality of the submission (*Lancet* 1999; **354**: 1896–900). Potential authors are advised to contact: Mr J. A. Murie, University Department of Surgery, The Royal Infirmary, Edinburgh EH3 9YW, UK.

Leading articles

The Editors commission leading articles that are 600–900 words in length and address controversial topics of current interest. They should be supported by no more than ten key references. Submissions may be subjected to external review and assessment by the Editorial Board before acceptance. The Editors retain the right to alter style and shorten material for publication. An honorarium is payable on publication.

Correspondence

The Editors welcome topical correspondence. Letters should not exceed 250 words and should be typed double-spaced.

Typescripts

Manuscripts must be clearly reproduced with adequate space for editorial notes. Present the text on one side of sheets of A4 paper (210 × 297 mm) with double spacing and 4-cm margins. **Begin each section (abstract, introduction, patients and methods, results and discussion) on a new page. Manuscripts that do not conform to these requirements will be returned for recasting.**

Title page

On the title page give: (1) the title of the article; (2) the name and initials of each author; (3) the department and institution to which the work should be attributed; (4) **the name, postal and email addresses, telephone and facsimile numbers of the author responsible for correspondence and to whom requests for reprints should be addressed;** (5) sources of financial support; and (6) the category in which the manuscript is being submitted (original article, review, etc).

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This must not exceed 200 words and should be presented in a structured format. **Background**: state why the study was done and its main aim. **Method**: describe patients, laboratory material and other methods used. Clearly identify the nature of the study, i.e. randomized controlled trial, retrospective review, experimental study, etc. **Results**: state the main findings including important numerical values. **Conclusion**. state the main conclusions but controversial or unexpected observations may be highlighted.

Tables and illustrations

Submit four copies of all illustrations and tables. Type each table on a separate page with a brief title. Line drawings are acceptable as clear black on white graphics, computer print-out or photocopies. Submit radiographs, photomicrographs, etc unmounted in the form of glossy prints, original transparencies or negatives. Illustrations in colour are encouraged and will be printed at no cost to the author. If you include photocopies, they should be of sufficient quality to enable the Journal's referees to judge their content and value. Label each illustration on the reverse side giving its number (to correspond with its reference in the text) and the name(s) of the author(s); indicate the top of the illustration. Include a measure of magnification of photomicrographs. Include explanations of symbols and shading within the figure. Survival curves must be accompanied by a table giving the actual numbers of patients involved. Include in the legends to illustrations and the footnotes to tables brief but comprehensive explanations of all the information presented. Look at recent issues of the Journal for examples of accepted layout. Any table or illustration reproduced from a published work must give the original source in full. You must obtain permission from the original author and the publisher before submission.

Abbreviations

Use abbreviations *sparingly*. Terms that are mentioned frequently may be abbreviated but only if this does not impair comprehension. Abbreviations must be used consistently and must be defined on first use.

Numbers and units

Use the decimal point, not a comma, for example 5·7. Use a space and not a comma after thousands and multiples thereof, for example 10 000. Use SI units (International System of Units) except for the measurement of blood pressure (mmHg).

Statistics

For detailed guidance on the handling of statistical material consult *Br J Surg* 1991; **78**: 782–4. In evaluating a manuscript the Editors and statistical referees will consider the design of the study, the presentation and analysis of data and the interpretation of results.

Design

Set out clearly the objectives of the study, identify the primary and secondary hypotheses, the chosen end-points and justify the sample size. Investigators embarking on randomized controlled studies may wish to consider the CONSORT statement (*JAMA* 1996; **276**: 637–9).

Presentation

Whenever possible use graphical presentation to illustrate the main findings of a study. The use of standard deviation and standard error should be clearly distinguished and presented in parentheses after the mean values.

Analysis

Clearly describe methods used for each analysis. Methods not in common usage should be referenced. Report results of statistical tests by stating the value of the test statistic, the number of degrees of freedom and the *P* value. Actual *P* values should be reported to two decimal places, especially when the result is not significant. The results of the primary analyses should be reported using confidence intervals instead of, or in addition to, *P* values.

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Take great care in your interpretations. Do not place undue emphasis on secondary analyses.

References

Type the references with double spacing in the Vancouver style (see **Preparation of manuscripts**). Reference to abstracts and personal communications is discouraged. Reference to unpublished communications will not be accepted.

In the text, number references consecutively by superscript:^{1} or $^{1-3}$. References cited only in tables or figures should be numbered in sequence.

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